09/20/04

AF/3731

Docket No.: 032405-065

September 17, 2004

Mail Stop Appeal Brief - Patents
Commissioner For Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Re:	Applicant(s):	Vargas, Jaime, et. al.	
	Assignee:	Cardica, Inc.	
	Title:	Device for Cutting and Anastomosing Tissue	
	Serial No.:	09/989,055	
	Examiner:	Julian W. Woo	Filed: November 21, 2001
	Docket No.:	032405-065	Group Art Unit: 3731

Dear Sir:

Transmitted herewith are the following documents in the above-identified application:

(1) Return Receipt Postcard;
(2) This Transmittal Letter;
(3) Notice of Appeal; and
(4) Check no. 10451 in the amount of $165.00.

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Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Vargas, Jaime; et. al.		
Assignee:	Cardica, Inc.		
Title:	Device for Cutting and Anastomosing Tissue		
Serial No.:	09/989,055	Filing Date:	November 22, 2001
Examiner:	Julian W. Woo	Group Art Unit:	3731
Docket No.:	032405-065		

September 17, 2004

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APPEAL BRIEF UNDER 37 CFR § 1.192

This Appeal Brief is prepared and submitted pursuant to the Notice of Appeal filed in this case on August 13, 2004, in accordance with the new requirements of 69 Fed. Reg. 19960.

I. REAL PARTY IN INTEREST

The real party in interest is the assignee, Cardica, Inc., as named in the caption above.

II. RELATED APPEALS AND INTERFERENCES

No prior or pending appeals, interferences or other judicial proceedings are known to Appellant, Appellant's legal representative, or assignee which may be related to, directly affect or be directly affected by, or have a bearing on the decision by the Board of Patent Appeals in this appeal.

III. STATUS OF CLAIMS

Claims 34, 43-46, 50, 58, 59, 61 and 62 stand finally rejected. These claims are set forth in the appendix attached hereto.

Claims 51-54 have been objected to. These claims are not at issue and are not set forth in the appendix attached hereto.

IV. STATUS OF AMENDMENTS

No amendments were filed after final rejection or are currently pending in this case.

V. SUMMARY OF THE INVENTION

Claim 34 is directed to a device for performing an anastomosis procedure between a graft vessel and a target vessel, where that device includes a deployment tool (150, 160); an anastomosis device (120) detachably connected to the deployment tool (150, 160) and the anastomosis device (120) deformable to a deployed state; a sheath (352) connected to the deployment tool (150, 160); and a cutting element (350) connected to the sheath (352), the cutting element (350) configured to form an opening in the wall of the target vessel; wherein the deployment tool (150, 160) is configured to place the anastomosis device (120) at least partly into the opening and deploy the anastomosis device (120) to the deployed state, and the sheath (352) is removed from the opening outside of the graft vessel.[1] In this way, the anastomosis device connects the graft vessel to the target vessel in a manner that allows fluid to flow between them.

[1] *E.g.*, Specification, page 3, lines 1-9; page 4, line 23 through page 6, line 2; page 9, line 1 through page 17, line 24; page 24, line 21 through page 25, line 11; Figures 1-8, 27 (exemplary reference characters indicated in text above). The sheath is misnumbered in the specification at page 24, line 24.

Claim 43 is directed to a device for piercing the wall of a target vessel, where that device includes a tubular sheath (352) having an edge at its distal end; a cutting element (350) slidable within the tubular sheath (352); and a cable (356, 396) attached to the cutting element (350); wherein the cutting element (350) is insertable through the wall of the target vessel and retractable by the cable (356, 396) to compress the wall of the target vessel against the edge, wherein a portion of the wall of the target vessel is removed.[2] In this way, a cutting element actuated by a cable creates an opening in the wall of the target vessel. Claims 44-46 and 50 depend from independent claim 43, and thus add additional limitations to those present in independent claim 43.

Claim 58 is directed to a device for piercing the wall of a target vessel and removing a tissue ring therefrom, where the device includes a tubular sheath (352, 384, 390) including a lumen therein; and a cutting element (350, 392) slidable within the tubular sheath (352, 384, 390), wherein the cutting element (350, 392) cooperates with the tubular sheath (352, 384, 390) to remove the tissue ring from the wall of the target vessel and move the tissue ring out of the lumen.[3] In this way, the tissue ring is moved out of the lumen of the sheath such that it does not block that lumen. Claims 59 and 61-62 depend from independent claim 58, and thus add additional limitations to those present in independent claim 58.

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[2] *E.g.*, Specification, page 3, lines 1-14; page 24, line 21 through page 27, line 27; Figures 27-28; 38A-39C (exemplary reference characters indicated in text above). The sheath is misnumbered in the specification at page 24, line 24.

[3] *E.g.*, Specification, page 17, line 25 through page 18, line 11; page 24, line 21 through page 28, line 16; Figures 27-34, 38A-40C (exemplary reference characters indicated in text above). The sheath is misnumbered in the specification at page 24, line 24.

VI. ISSUES

A. Claim 34

Independent claim 34 stands finally rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,221,259 to Weldon *et. al.* ("Weldon").

B. Claims 43-46 and 50

Independent claim 43 stands finally rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 5,893,369 to LeMole ("LeMole"). Claims 44-46 and 50 depend from claim 43.

C. Claims 58-59 and 61-62

Independent claim 58 stands finally rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,403,338 to Milo ("Milo").

VII. ARGUMENTS

A. The Cited Art Does Not Read on Claim 34

The MPEP sets forth the legal standard of anticipation under 35 U.S.C. §102: "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."[4] (emphasis added).

Claim 34 claims a "device for performing an anastomosis procedure between a graft vessel and a target vessel, comprising: a deployment tool; an anastomosis device detachably connected to said deployment tool, said anastomosis device deformable to a deployed state; and a sheath connected to said deployment tool; and a cutting element connected to said sheath, said cutting element configured to form an opening in the wall of the target vessel;

wherein said deployment tool is configured to place said anastomosis device at least partly into the opening and deploy said anastomosis device to the deployed state, and said sheath is removed from the opening outside of the graft vessel."

First, the meaning of the claim term "anastomosis device" must be established. A claim term is given "the full range of its ordinary meaning as understood by persons skilled in the relevant art."[5] Reference materials that are "publicly available at the time the patent is issued are objective resources that serve as reliable sources of information on the established meanings that would have been attributed to the terms of the claims by those of skill in the art."[6] Such reference materials include "dictionaries, encyclopedias and treatises."[7]

Turning to the dictionary, the term "anastomosis" means "[o]perative union of two hollow tubular structures" in the surgical context.[8] The term "operative" can mean "[r]elating to, or effected by means of an operation," or "[a]ctive, effective."[9] As used in the surgical context, particularly for coronary artery bypass graft (CABG) surgery, the term has both meanings. The surgical anastomosis connects two hollow tubular structures by means of a surgical operation, and does so in an effective manner that allow blood to flow therebetween.

This dictionary definition requires that the union of the two hollow tubular structures is "operative," which means "active" or "effective." In order for an anastomosis to be effective, there must be substantially free flow of a fluid between the two hollow tubular structures. Published reference materials, including papers published in peer-reviewed journals, support this definition of "operative." As one example, FitzGibbon et. al. have

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[4] MPEP 2131 (*quoting Verdegaal Brothers v. Union Oil of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)).
[5] *Texas Digital Systems, Inc. v. Telegenix, Inc.*, 2002 U.S. App. LEXIS 21567, *10 (Fed. Cir. 2002).
[6] *Id.* at *12.
[7] *Id.*
[8] WEBSTER'S NEW WORLD/STEDMAN'S CONCISE MEDICAL DICTIONARY 35 (1987) (Exhibit 1).
[9] *Id.* at 527 (Exhibit 1).

developed a grading system to define anastomotic patency for bypass grafts utilized in CABG procedures.[10] The term "patency" means "[t]he state of being freely open or patulous."[11] The term "patulous" means "[p]atent," which in turn means "[p]atulous; open; exposed."[12] Thus, bypass graft patency refers to the state of the bypass graft being freely open at its ends and along its length.

In the Fitzgibbon grading system, each graft in a CABG procedure is assigned one of three grades: A, which is an "[e]xcellent graft with unimpaired runoff"; B, which has "[s]tenosis reducing caliber of proximal or distal anastomosis or trunk to <50% of the grafted coronary artery"; or O, which is "occlusion" of the graft.[13] Occlusion is "the state of being closed," and thus an occluded graft is closed to flow therethrough.[14] Patency is the desired result, whereas occlusion of the graft is undesirable. Indeed, the U.S. Food and Drug Administration (FDA) identifies "occlusion" as a "problem" associated with anastomosis that can result in death or injury.[15]

The greater the patency of the graft, the better the anastomosis.[16] That is, the goal of the anastomosis is free flow between the two hollow tubular structures joined together. Thus, to obtain an "operative union" of two hollow tubular structures, as anastomosis is defined, the junction between those two hollow tubular structures must be patent. That is, a completed

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[10] Gerald M. Fitzgibbon *et. al.*, *Coronary Bypass Graft Fate: Long-Term Angiographic Study*, 17 J. AM. C. CARDIOLOGY, 1075, 1076 (1991) (Exhibit 2); Gerald M. Fitzgibbon *et. al.*, *Coronary Bypass Graft Fate and Patient Outcome: Angiographic Follow-Up of 5,065 Grafts Related to Survival and Reoperation in 1,388 Patients During 25 Years*, 28 J. AM. C. CARDIOLOGY 616, 618 (1996) (Exhibit 3).

[11] WEBSTER'S NEW WORLD/STEDMAN'S CONCISE MEDICAL DICTIONARY 556 (1987) (Exhibit 1).

[12] *Id.* at 556-557 (Exhibit 1).

[13] 28 J. AM. C. CARDIOLOGY at 618 (Exhibit 3).

[14] WEBSTER'S NEW WORLD/STEDMAN'S CONCISE MEDICAL DICTIONARY 519-520 (1987) (Exhibit 1).

[15] Julia Marders, *Aortic Anastomosis Devices Adverse Event Report Analysis* 8, 10, *at* http://www.fda.gov/ohrms/dockets/ac/04/briefing/4029b2_01_fda%20presentation.ppt (Exhibit 4).

[16] 17 J. AM. C. CARDIOLOGY at 1078 (Exhibit 2); 28 J. AM. C. CARDIOLOGY AT 619 (Exhibit 3); Peter A. Seirafi, *Surgery for Coronary Artery Disease*, JACKSONVILLE MED. Oct. 2001, http://www.dcmsonline.org/jax-medicine/2001journals/Oct2001/cadsurgery.htm (Exhibit 5).

anastomosis allows substantially free flow between two hollow tubular structures. The Fitzgibbon grading system is one of a set of "standard criteria" for measuring the quality of an anastomosis, indicating that it, and what it measures, are understood and accepted by those skilled in the art.[17] Thus, the patency measured by the FitzGibbon grading system is well understood by those skilled in the art to be the desired outcome of anastomosis. As a result, to be effective, the "union" between two hollow tubular structures in an anastomosis must allow substantially free flow between those structures. Consequently, medical dictionaries and the published literature in the art establish that "anastomosis" means "a union of two hollow tubular structures that allows substantially free flow between those structures."

This definition is consistent with definitions of anastomosis from other non-dictionary sources. For example, the online Medical Education Glossary of Summa Heath System defines anastomosis as "[t]he surgical joining of two ducts or blood vessels to allow flow between them."[18] As another example, WordNet of the Cognitive Sciences Laboratory of Princeton University defines anastomosis as "a natural or surgical joining of parts or branches of tubular structures so as to make or become continuous."[19]

This definition is also consistent with the specification of the present application, which states that "anastomosis is a procedure by which two blood vessels within a patient are surgically joined together."[20] Anastomosis may be performed to treat coronary artery disease, which "involves the grafting of a vessel in the form of a prosthesis or harvested artery or vein to reroute blood flow around the occlusion and restore adequate blood flow to the heart

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[17] Antonis A. Pitsis *et. al.*, *Coronary Artery Bypass Grafting for Multi-Vessel Coronary Disease on the Beating Heart: Comparative Study of 500 Patients*; 43 HELLENIC J. CARDIOLOGY 26, 29-30 (2002) (Exhibit 6).

[18] Summa Health System, Medical Education Glossary, http://www.summahealth.org/common/templates/glossary.asp?id=2746&page=A (last visited Sep. 14, 2004) (Exhibit 7).

[19] WordNet, Cognitive Science Laboratory of Princeton University http://www.cogsci.princeton.edu/cgi-bin/webwn?stage=1&word=anastomosis (last visited Sep. 14, 2004) (Exhibit 8)

muscle. This treatment is known as coronary artery bypass grafting (CABG)."[21] (emphasis added).

The term "anastomosis device" is well-known, and has been utilized by those skilled in the art for some time. An anastomosis device is a device that is utilizes to perform anastomosis. Thus, based on the definition of "anastomosis" as a union of two hollow tubular structures that allows substantially free flow between those structures, as established above, an "anastomosis device" is a device that unites two hollow tubular structures to allow substantially free flow between those structures.

As one example, agencies of the Federal Government concur that the term "anastomosis device" is standard in the art, and refers to a device that unites two hollow tubular structures to allow substantially free flow between those structures. "Anastomosis devices" is an acceptable identification of goods in the Trademark Office according to the Acceptable Identification of Goods and Services manual.[22] Further, the Food and Drug Administration (FDA) utilizes the term to describe a device that takes the places of a sutured anastomosis in a CABG procedure.[23]

As another example, manufacturers utilize the term "anastomosis device" to refer to a device that unites two hollow tubular structures to allow substantially free flow between those structures. Attached is a printout of a web page from St. Jude Medical in regard to its Symmetry™ Bypass System Aortic Connector, characterizing that device as "a mechanical

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[20] Specification; page 1, lines 8-9.

[21] Specification; page 1, lines 13-16.

[22] ACCEPTABLE IDENTIFICATION OF GOODS AND SERVICES MANUAL, http://tess2.uspto.gov/netacgi/nph-brs?sect2=THESOFF&sect3=PLURON&s1=anastomosis+device&l=MAX&sect1=IDMLICON&sect4=HITOFF&op1=AND&d=TIDM&p=1&u=%2Fnetahtml%2Ftidm.html&r=0&f=S (Exhibit 9).

[23] Marders, *supra* note 13, at 14, 27 (Exhibit 4).

anastomosis device that allows cardiac surgeons to attach saphenous vein grafts to the aorta without sutures."[24] (emphasis added).

As another example, business analysts and investors utilize the term "anastomosis device" to refer to a device that unites two hollow tubular structures to allow substantially free flow between those structures. Attached is a printout of an abstract from an issue of "Start-Up: Windhover's Review of Emerging Medical Ventures," characterizing "anastomosis devices" as "hot technology," and emphasizing the importance of patency to the acceptance of those devices.[25] Also attached is a printout from a web page from the National Collegiate Inventors & Innovators Alliance, describing a grant given in 1999 to a Simple Anastomosis Device Team at Stanford University.[26] The grant to the Simple Anastomosis Device Team is to "develop and prototype a device that joins grafted blood vessels to host vessels in cardiac bypass surgery."[27]

As another example, researchers utilize the term "anastomosis device" to refer to a device that unites two hollow tubular structures to allow substantially free flow between those structures. Reuthebuch et. al. utilized the Symmetry "mechanical anastomosis device" to perform "vein-to-aorta anastomosis" in CABG procedures.[28] These researchers found that significant occlusion resulted from the use of these connectors, and discontinued their use at

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[24] http://symmetry.sjm.com/ourbkrnd.htm (last visited Sep. 14, 2004) (Exhibit 10).

[25] David Cassak, *Lining Up Anastomosis Opportunities*(abstract), START-UP: WINDHOVER'S REVIEW OF EMERGING MEDICAL VENTURES, March 1, 2002, http://sis.windhover.com/windbuy/lpext.dll/windbuy/su/2002/2002900049.htm (Exhibit 11).

[26] *Advanced E-Team Grant Profile*, http://apps.nciia.net/WebObjects/NciiaResources.woa/wa/View/GrantProfile?n=1000269 (last visited Sep. 14, 2004) (Exhibit 12).

[27] *Id.*

[28] O. Reuthebuch *et. al.*, *Early bypass occlusion after deployment of nitinol connector devices* (abstract); 127(5) J. THORACIC CARDIOVASCULAR SURGERY 1421 (2004), http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15116002 (Exhibit 13).

their institution, confirming that closure of the anastomosis is undesirable and a poor patient outcome.[29]

The definition of "anastomosis device" as a device that unites two hollow tubular structures to allow substantially free flow between those structures is consistent with the specification of the present application, which states that an anastomosis device used in a CABG procedure connects "the end of a graft vessel to a target vessel at the site of [an] incision" made in the wall of the target vessel. (*e.g.*, specification; page 3, lines 2-5). Thus, usage of the term "anastomosis device" is commonplace in the art, and its definition as a device that unites two hollow tubular structures to allow substantially free flow between those structures is well accepted.

Turning to the rejection of claim 34 in the Final Office Action of July 19, 2004 ("Final Action"), Weldon does not expressly or inherently describe each and every element of claim 34. First, the clotting agent 34 disclosed in Weldon is a chemical such as thrombin, in "foam, powder or jell [sic] form."[30] A "foam, powder or jell" is not a structure or mechanism. Rather, it is simply a quantity of chemical in a particular state. Thus, the clotting agent 34 of Weldon is no device, much less an anastomosis device. Additionally, a chemical is not "deformable," as required by claim 34. Thus, Weldon provides no written description nor enablement for the claimed "anastomosis device deformable to a deployed state."

Second, Weldon does not operatively unite two separate hollow tubular structures, hollow or otherwise, whether utilizing an anastomosis device or not. As established above, an "anastomosis device" is a device that unites two hollow tubular structures to allow substantially free flow between those structures. Weldon identifies only a single hollow

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[29] *Id.*

[30] Weldon, col. 4, line 65 through col. 5, line 8.

tubular structure, the artery F.[31] The clotting agent 34 closes an aperture A of that single artery F, to "greatly hasten clotting and prevent further bleeding from the aperture A."[32] No graft vessel or any other hollow tubular structure in addition to the single artery F is disclosed. Thus, Weldon does not disclose two hollow tubular structures that can be operatively united. Consequently, Weldon does not and cannot disclose the claimed "device for performing an anastomosis procedure between a graft vessel and a target vessel."

Third, Weldon does not provide for substantially free flow between two hollow tubular structures. Indeed, Weldon teaches away from flow between vessels altogether, by disclosing the clotting agent that acts to close an aperture A of an artery to "greatly hasten clotting and prevent further bleeding from the aperture A."[33] That is, Weldon "relates, in general, to devices and methods for stopping an undesirable flow of fluid."[34] (emphasis added). In contrast, claim 34 claims, among other items, an anastomosis device, which as established above means a device that unites two hollow tubular structures to allow substantially free flow between those structures. Thus, Weldon does not and cannot disclose the claimed "anastomosis device." Indeed, Weldon teaches away from allowing substantially free flow, by teaching devices and methods for stopping flow.

Fourth, construction of the term "anastomosis device" to include a structure or chemical for closing an aperture would result in claim 34 failing to read on the preferred embodiment. As a "general rule" of construction, "claims...are not limited to a preferred embodiment.[35] However, the Federal Circuit has emphasized that "it is axiomatic that a claim

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[31] Weldon, col. 3, lines 58-60; col. 4, lines 1-3; col. 5, lines 32-65; col. 6, lines 3-6; Figures 1, 5-7.

[32] Weldon, col. 5, lines 63-65.

[33] Weldon, col. 5, lines 63-65.

[34] Weldon, col. 1, lines 10-14.

[35] *E.g.*, *Anchor Wall System, Inc. v. Rockwood Retaining Walls, Inc.*, U.S. App. Lexis 16536, *20-21; 340 F.3d 1298 (Fed. Cir. 2003); *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998).

construction that excludes a preferred embodiment...'is rarely, if ever correct.'"[36] (emphasis added). In the present application, the preferred embodiment is the embodiment of the elected species. As set forth in the First Office Action, the elected species is that shown in Figure 27 and described in the accompanying text.[37] This species is an embodiment of a trocar arrangement that is a component assembly of a deployment system 150 that includes an anastomosis device.[38] Nowhere in Figure 27 or in the associated text is it disclosed that an anastomosis device closes an aperture in any tissue at all, much less in a hollow tubular structure. In direct contract, in the preferred embodiment "the opening is expanded by expansion of the anastomosis device."[39] (emphasis added). Further, as established above, an anastomosis device is a device that unites two hollow tubular structures to allow substantially free flow between those structures. Thus, in the preferred embodiment, the anastomosis device enables free flow between the graft vessel and the target vessel through the expanded opening in the target vessel. If the term "anastomosis device" is construed to include chemicals for closing an aperture in a vessel, then that interpretation excludes the preferred embodiment from the scope of claim 34, in violation of the axiomatic claim construction rules

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[36] *Anchor Wall System* at *21, (*quoting Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996)) (emphasis added); *Moba, B.V. v. Diamond Automation, Inc.*, 2003 U.S. App. Lexis 6285, *20, 325 F.3d 1306 (Fed. Cir. 2003) (*quoting Vitronics,* 90 F.3d at 1583) ("a claim interpretation that puts the preferred embodiment outside the claim is 'rarely, if ever correct'"); *National Steel Car, Ltd. v. Canadian Pacific Railway, Ltd.*, 2004 U.S. App. Lexis 1346, *48, 357 F.3d 1319 (Fed. Cir. 2004) (*quoting Vitronics,* 90 F.3d at 1583) ("[c]laim interpretations that do not read on the preferred embodiment are 'rarely, if ever correct'"); *Gentry Gallery*, 134 F.3d at 1477 (*quoting Vitronics,* 90 F.3d at 1583); *International Rectifier Corp. v. Ixys Corp.*, 2004 U.S. App. Lexis 5164, *18, 361 F.3d 1363 (Fed. Cir. 2004) (*quoting Gentry Gallery*, 134 F.3d at 1477); *Glaxo Group Ltd. v. Apotex, Inc.*, 2004 U.S. App. Lexis 15489, *17, 376 F.3d 1339 (Fed. Cir. 2004) (*quoting Vitronics,* 90 F.3d at 1583) (defendant's proposed claim construction "violates the principle that claims should rarely, if ever, be construed to exclude a preferred embodiment"); *Globetrotter Software, Inc. v. Elan Computer Group, Inc.*, 2004 U.S. App. Lexis 5428, *39, 362 F.3d 1367 (*quoting Vitronics,* 90 F.3d at 1583).

[37] First Office Action, March 24, 2004 ("First Action"), page 2; *e.g.*, Specification, page 24, line 21 through page 25, line 11.

[38] *E.g.*, Specification, page 14, lines 19-24.

[39] Specification, page 25, lines 10-11.

set out by the Federal Circuit. Thus, the term "anastomosis device" cannot include a chemical for closing an aperture in a vessel.

Fifth, construction of the term "anastomosis device" to include a structure or chemical for closing an aperture would result in claim 34 failing to read on any embodiment described in the specification at all. "Although the specification need not present every embodiment or permutation of the invention and the claims are not limited to the preferred embodiment...neither do the claims enlarge what is patented beyond what the inventor has described as the invention."[40]

Not only does the preferred embodiment not disclose that an anastomosis device closes an opening in tissue, but also the entire specification does not disclose that an anastomosis device closes an opening in tissue. The specification consistently refers to the connection of the graft vessel to the target vessel by an anastomosis device inserted into the opening in the target vessel, thereby allowing flow therebetween.[41] The specification says nothing about utilizing an anastomosis device, a device that a device that unites two hollow tubular structures to allow substantially free flow between those structures, for closing an opening. To construe the term "anastomosis device" to include a chemical for closing an aperture in a vessel would be to enlarge the scope of claim 34 beyond what has been described as the invention, contrary to law. Thus, the term "anastomosis device" does not and cannot encompass a chemical for closing an aperture in a vessel.

Thus, each and every element of claim 34 is not set forth in Weldon, and claim 34 is not anticipated by Weldon. Therefore, the rejection should be reversed by the Board. Claim

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[40] *Network LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001); *Biogen, Inc. v. Berlex Laboratories, Inc.*, 2003 U.S. App. Lexis 1721, *22, 318 F.3d 1132 (Fed. Cir. 2003) (*quoting Network*, 242 F.3d at 1352).

[41] *E.g.*, Specification, page 4, line 26 through page 5, line 2.

34 is generic.[42] Thus, upon reversal of the rejection of claim 34, claim 34 is allowable as to all species.

B. The Cited Art Does Not Read on Claims 43-46 or 50

Claim 43 claims a "device for piercing the wall of a target vessel, comprising: a tubular sheath having an edge at its distal end; a cutting element slidable within said tubular sheath; and a cable attached to said cutting element; wherein said cutting element is insertable through the wall of the target vessel and retractable by said cable to compress the wall of the target vessel against said edge, wherein a portion of the wall of the target vessel is removed."

In contrast, LeMole does not expressly or inherently describe each and every element of claim 43. The Final Action states that LeMole discloses "a cable (38) connected to the cutting element."[43] However, nowhere does LeMole disclose a cable, whether or not attached to a cutting element such that the cutting element is retractable by the cable. Thus, LeMole provides no written description, and no enablement, for "a cable attached to said cutting element; wherein said cutting element is insertable through the wall of the target vessel and retractable by said cable to compress the wall of the target vessel."

Further, the structure in LeMole identified with callout number 38 is a block handle. The block handle 38 is connected to and extends proximally from the block 32, and can be actuated by hand.[44] Alternately, the distal end of the block handle 38 may be attached to an actuation mechanism to permit single-handed actuation of the block 32 along with the punch 30.[45] Thus, the block 32 is actuated by motion of the block handle 38, which motion may be

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[42] First Action, page 3.

[43] Final Action, pages 2-3.

[44] *E.g.*, LeMole, col. 6, lines 60-65; Figures 6-8, 9B, 9C.

[45] LeMole, col. 7, lines 4-7.

caused by hand or by a mechanism. That is, force exerted by hand or by an actuation mechanism is exerted indirectly on the block 32 via the block handle 38.

Initially, the block 32 is positioned outside the vessel 12.[46] The actuation of the block 32 includes two motions. First, the block 32 "is inserted through the cut in the vessel wall and into the lumen of the vessel 12" in a distal direction.[47] Second, "the block 32 is translated toward the punch 30" in a proximal direction.[48] The actuation of the block 32 in each direction is performed by the block handle 38. If the block handle 38 were a cable, the block handle 38 would be incapable of performing the first motion of pushing the block 32 distally through the cut in the vessel wall and into the lumen of the vessel 12. This is because a cable has strength in tension, but no strength in compression; "pushing on a cable is a little like pushing on a wet noodle."[49] Indeed, where the block 32 includes a sharp cutting edge 34 that cuts through the vessel wall, even more force would have to be transmitted in compression through the block handle 38 to the block 32 in order to push the cutting edge 34 through the vessel wall.[50] Thus, the block handle 38 cannot be a cable; if it were, the device of LeMole would be inoperative.

If the rejection of claim 43 over LeMole was an inherency rejection that was not expressly identified as such, that rejection still fails for the reasons set forth above. In addition, an inherency rejection must be supported: "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of

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[46] *E.g.*, LeMole, Figure 6.

[47] LeMole, col. 6, lines 24-26; Figure 7.

[48] LeMole, col. 6, lines 28-30; Figure 8.

[49] University of Utah Structural Engineering Department; http://www.civil.utah.edu/~blaser/MM_project/structures/types.htm). (last visited Sep. 14, 2004) (Exhibit 14).

[50] LeMole, col. 6, lines 39-44; Figures 6, 9C.

the applied prior art."[51] (emphasis in original). No such support was set forth in the Final Action.

Thus, each and every element of claim 43 is not set forth in LeMole, and claim 43 is not anticipated by LeMole. Therefore, the rejection should be reversed by the Board. Claims 44-46 and 50 depend from claim 43 and thereby include its limitations, and are thus patentable for at least the same reasons as claim 43.

C. The Cited Art Does Not Read on Claims 58-59 or 61-62

Claim 58 claims a "device for piercing the wall of a target vessel and removing a tissue ring therefrom, comprising: a tubular sheath including a lumen therein; and a cutting element slidable within said tubular sheath, wherein said cutting element cooperates with said tubular sheath to remove the tissue ring from the wall of the target vessel and move the tissue ring out of said lumen."

Referring to the specification and the drawings, the tubular sheath 352 has a lumen therein.[52] The cutting element 350 cooperates with the sheath 352 to remove a tissue ring from the wall of the target vessel.[53] The cutting element 350 further cooperates with the sheath 352 to remove to the tissue ring from the lumen of the sheath 352, such as through an opening 354 in the side of the sheath 352.[54] In this way, the cutting element 350 and the tissue ring do not block the lumen of the sheath 352, such that an anastomosis device and/or other tools or devices may be transported through the lumen of the sheath 352.[55]

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[51] MPEP 2112 (*citing Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)).

[52] Specification, page 24, line 21 through page 25, line 1; Figure 27.

[53] Specification, page 24, line 24 through page 25, line 1; page 25, lines 6-7; Figure 27.

[54] *E.g.*, Specification, page 24, lines 21-24; page 26, lines 3-5; Figure 27.

[55] *E.g.*, Specification, page 26, lines 22-24; page 18, lines 2-3 ("the trocar includes a tubular member through which the anastomosis device is delivered").

In contrast, Milo does not expressly or inherently describe each and every element of claim 58. Milo describes a tube 1 having a knife edge 9 at its distal end.[56] A disc 7 is worked through tissue, after which the knife edge 9 is advanced toward the disc 7 to cut tissue and form an aperture in the tissue.[57] Milo neither discloses nor suggests anything about the disposition of the tissue that is cut from the vessel wall in order to form the aperture. The tube 1 is a simple right cylindrical tube that includes no provision for moving the tissue cut by the cutting edge 9 and the disc 7 out of the lumen of the tube. Thus, Milo provides no written description, and no enablement, for a cutting element that cooperates with a tubular sheath to remove the tissue ring from the wall of the target vessel and move the tissue ring out of the lumen of the sheath. Although "pictures and drawings may be sufficiently enabling," the figures of Milo show no feature or features that would allow a cutting element that cooperates with a tubular sheath to remove the tissue ring from the wall of the target vessel and move the tissue ring out of the lumen of the sheath.[58] Indeed, the figures of Milo show a needle tube 2 and/or outlet 4 within the tube 1, which are structures that would bar the motion of tissue out of the proximal end of the tube 1—the only opening that might allow motion of tissue out of the lumen of the sheath.[59] Thus, Milo teaches away from a device having a "cutting element [that] cooperates with said tubular sheath to remove the tissue ring from the wall of the target vessel and move the tissue ring out of said lumen."

Further, claim 58 requires that the cutting element is "slidable within said tubular sheath." If the cutting element is considered to be the edge 9 at the distal end of the tube 1, it is fixed relative to the tube 1, and not slidable relative to anything. If the cutting element is

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[56] Milo, col. 2, lines 16-17; Figure 1.

[57] *E.g.*, Milo, col. 2, lines 10-17, 22-46; Figure 1.

[58] MPEP 2121.04.

[59] *E.g.*, Milo; col. 2, lines 10-22; Figures 1, 2.

considered to be the disc 7, Milo discloses moving that disc 7 outside of the tube 1 relative to the edge 9, and discloses nothing about that disc 7 being slidable within the tube 1. Indeed, nowhere does Milo disclose or suggest that the disc 7 has a diameter less than the edge 9, which it must have to enter the lumen of the tube 1 such that it could be slidable within the tube 1.

If the rejection of claim 58 over Milo was an inherency rejection that was not expressly identified as such, that rejection still fails for the reasons set forth above. In addition, an inherency rejection must be supported: "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art."[60] (emphasis in original). No such support was set forth in the Final Action.

Thus, each and every element of claim 58 is not set forth in Milo, and claim 58 is not anticipated by Milo. Therefore, the rejection should be reversed by the Board. Claims 59 and 61-62 depend from claim 58 and thereby include its limitations, and are thus patentable for at least the same reasons as claim 58.

[60] MPEP 2112 (*citing Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990))

VII. CONCLUSION

For the above reasons, Applicants respectfully submit that the Final Action's rejection of pending Claims 34, 43-46, 50, 58, 59, 61 and 62 was unfounded. Accordingly, Applicants request that the rejection of Claims 34, 43-46, 50, 58, 59, 61 and 62 be reversed.

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APPENDIX 1 -CLAIMS

34. A device for performing an anastomosis procedure between a graft vessel and a target vessel, comprising:

a deployment tool;

an anastomosis device detachably connected to said deployment tool, said anastomosis device deformable to a deployed state; and

a sheath connected to said deployment tool; and

a cutting element connected to said sheath, said cutting element configured to form an opening in the wall of the target vessel;

wherein said deployment tool is configured to place said anastomosis device at least partly into the opening and deploy said anastomosis device to the deployed state, and said sheath is removed from the opening outside of the graft vessel.

43. A device for piercing the wall of a target vessel, comprising:

a tubular sheath having an edge at its distal end;

a cutting element slidable within said tubular sheath; and

a cable attached to said cutting element;

wherein said cutting element is insertable through the wall of the target vessel and retractable by said cable to compress the wall of the target vessel against said edge, wherein a portion of the wall of the target vessel is removed.

44. The device of Claim 43, wherein said cutting element comprises:

a tapered tip;

an anvil surface behind said tapered tip; and

a shaft extending from said anvil surface.

45. The device of Claim 43, wherein said edge is substantially circumferential.

46. The device of Claim 43, wherein said cutting element comprises at least two pieces.

50. The device of Claim 43, wherein a storage position is defined relative to said tubular sheath, and wherein said cutting element is movable to said storage position.

58. A device for piercing the wall of a target vessel and removing a tissue ring therefrom, comprising:

a tubular sheath including a lumen therein; and

a cutting element slidable within said tubular sheath, wherein said cutting element cooperates with said tubular sheath to remove the tissue ring from the wall of the target vessel and move the tissue ring out of said lumen.

59. The device of Claim 58, wherein said cutting element traps and retains the tissue ring.

61. The device of claim 58, wherein at least part of the distal end of said tubular sheath is sharpened.

62. The device of claim 58, wherein the distal end of said cutting element is tapered.

APPENDIX 2 – EVIDENCE APPENDIX

Exhibit 1..... WEBSTER'S NEW WORLD/STEDMAN'S CONCISE MEDICAL DICTIONARY 35, 519-520, 527, 556-557 (1987)

Exhibit 2..... Gerald M. Fitzgibbon *et. al.*, *Coronary Bypass Graft Fate: Long-Term Angiographic Study*, 17 J. AM. C. CARDIOLOGY, 1075, 1076 (1991)

Exhibit 3..... Gerald M. Fitzgibbon *et. al.*, *Coronary Bypass Graft Fate and Patient Outcome: Angiographic Follow-Up of 5,065 Grafts Related to Survival and Reoperation in 1,388 Patients During 25 Years*, 28 J. AM. C. CARDIOLOGY 616, 618 (1996)

Exhibit 4..... Julia Marders, *Aortic Anastomosis Devices Adverse Event Report Analysis* 8, 10, *at* http://www.fda.gov/ohrms/dockets/ac/04/briefing/4029b2_01_fda%20presentation.ppt

Exhibit 5..... Peter A. Seirafi, *Surgery for Coronary Artery Disease*, JACKSONVILLE MED. Oct. 2001, http://www.dcmsonline.org/jax-medicine/2001journals/Oct2001/cadsurgery.htm

Exhibit 6..... Antonis A. Pitsis *et. al.*, *Coronary Artery Bypass Grafting for Multi-Vessel Coronary Disease on the Beating Heart: Comparative Study of 500 Patients*; 43 HELLENIC J. CARDIOLOGY 26, 29-30 (2002)

Exhibit 7..... Summa Health System, Medical Education Glossary, http://www.summahealth.org/common/templates/glossary.asp?id=2746&page=A (last visited Sep. 14, 2004) (Exhibit 7).

Exhibit 8..... WordNet, Cognitive Science Laboratory of Princeton University http://www.cogsci.princeton.edu/cgi-bin/webwn?stage=1&word=anastomosis (last visited Sep. 14, 2004)

Exhibit 9..... ACCEPTABLE IDENTIFICATION OF GOODS AND SERVICES MANUAL, http://tess2.uspto.gov/netacgi/nph-brs?sect2=THESOFF&sect3=PLURON&s1=anastomosis+device&l=MAX&sect1=IDMLICON&sect4=HITOFF&op1=AND&d=TIDM&p=1&u=%2Fnetahtml%2Ftidm.html&r=0&f=S

Exhibit 10..... http://symmetry.sjm.com/ourbkrnd.htm (last visited Sep. 14, 2004)

Exhibit 11..... David Cassak, *Lining Up Anastomosis Opportunities*(abstract), START-UP: WINDHOVER'S REVIEW OF EMERGING MEDICAL VENTURES, March 1, 2002, http://sis.windhover.com/windbuy/lpext.dll/windbuy/su/2002/2002900049.htm

Exhibit 12..... *Advanced E-Team Grant Profile*, http://apps.nciia.net/WebObjects/NciiaResources.woa/wa/View/GrantProfile?n=1000269 (last visited Sep. 14, 2004)

Exhibit 13..... O. Reuthebuch *et. al.*, *Early bypass occlusion after deployment of nitinol connector devices* (abstract); 127(5) J. THORACIC CARDIOVASCULAR SURGERY 1421 (2004), http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15116002

Exhibit 14..... University of Utah Structural Engineering Department; http://www.civil.utah.edu/~blaser/MM_project/structures/types.htm). (last visited Sep. 14, 2004)

Webster's New World™/ Stedman's Concise Medical Dictionary

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tik). Relating to anaphy
:mely great sensitivity to
material.
ɔstance (antigen) capable of
susceptible to anaphylaxis
ıt will cause an anaphylactic
tized individual.
-tok'sin) [anaphylaxis +
A substance postulated to
of anaphylactic shock and
ılt from the *in vivo* combina
/ and the specific sensitizing
is injected as a shock dose

sis) [G. *ana*, away from
protection]. The immediate
unologic (allergic) reaction
ction of smooth muscle and
ıe to release of pharmacolog
(histamine, bradykinin, se
:ting substance), classically
nation of antigen (allergen
:ytophilic antibody (chiefl
e initiated, also, by relatively
ım aggregates (antigen-anti
ther) that seemingly activat
:o production of anaphyla

lowing inoculation of antige
ly sensitized to the specific
passive a.
e a.
temic a.; the immediate re
ɔoth muscles and capillaries
f a sensitized individual, that
ınd occasionally intracutane
:en (allergen).
ıte, transient kind of respons
ion of antigen (allergen) in
d individual and is limited
the site of inoculation.
n a.; a reaction resulting from
ı in an individual previously
ısly with specific antiserum
ıal.
lized a.
hylatoxin.
h) [G. *ana*, again, + plasis
ructural differentiation, esp
ost, but not all, malignan

ıg to anaplasty. 2. Characte
ıg to anaplasia. 3. Growth
cture.
ı-sis) [G. *ana*, back, + *apo*
acessory spinal process of
ially in the thoracic or lum

anaphia.

anarith'mia [G. *an-* priv. + *arithmos*, number]. Aphasia marked by inability to count or use numbers.

anar'thria [G. fr. *an-arthos*, without joints; (of sound) inarticulate]. Loss of the power of articulate speech.

anasarca (an'ă-sar'kah) [G. *ana*, through, + *sarx* (*sark-*), flesh]. A generalized infiltration of edema fluid into subcutaneous connective tissue.

anasar'cous. Characterized by anasarca.

anas'tomose. **1.** To open one structure into another directly or by connecting channels, said of blood vessels, lymphatics, and hollow viscera; also incorrectly applied to nerves. **2.** To unite by means of an anastomosis, or connection between formerly separate structures.

anastomo'sis, pl. **anastomo'ses** [G. *anastomōsis*, from *anastomoō*, to furnish with a mouth]. **1.** A natural communication, direct or indirect, between two blood vessels or other tubular structures; also incorrectly applied to nerves. **2.** Operative union of two hollow or tubular structures. **3.** An opening created by surgery, trauma, or disease between two or more normally separate spaces or organs.

antiperistaltic a., an a. diverting the normal flow of contents.

a. arterioveno'sa [NA], **arteriovenous a., arteriolovenular a.;** vessels through which blood is shunted from arterioles to venules without passing through the capillaries.

Billroth I and II a., Billroth's *operations* I and II.

conjoined a., the joining together of two small blood vessels by side-to-side elliptical a. to create a single larger stoma for subsequent end-to-end a.

cruciate a., crucial a., an a. between branches of the perforating, gluteal and circumflex femoral arteries located behind the upper part of the femur.

heterocladic a., a. between branches of different arteries.

H-graft a., a side-to-side grafting of adjacent vessels which utilizes a straight connecting conduit.

homocladic a., a. between branches of the same artery.

intestinal a., enteroenterostomy.

isoperistaltic a., an a. allowing flow of contents in the same and natural direction.

postcostal a., logitudinal a. of intersegmental arteries giving rise to the vertebral artery.

precostal a., longitudinal a. of intersegmental arteries giving rise to thyrocervical and costocervical trunks.

Riolan's a., a. of the superior and inferior mesenteric arteries.

Roux-en-Y a., a. of the distal end of the divided jejunum to the stomach, bile duct, or another structure, with implantation of the proximal end into the side of the jejunum at a suitable distance below the first a.

termino-terminal a., a. of the central end of an artery with the peripheral end of the corresponding vein, and the peripheral end of the artery with the central end of the vein.

anastomot'ic. Pertaining to an anastomosis.

anatomical (an'ă-tom'ī-kal). **1.** Relating to anatomy. **2.** Structural.

anat'omist. A specialist in the science of a anatomy.

anatomy (ă-nat'o-mī) [G. *anatomē*, dissection, from *ana*, apart, + *tomē*, a cutting]. **1.** The morphologic structure of an organism. **2.** The science of the morphology or structure of organisms.

applied a., the practical application of anatomical knowledge to diagnosis and treatment.

comparative a., the comparative study of animal structure in regard to homologous organs or parts.

dental a., that branch of gross a. concerned with the morphology of teeth, their location, position, and relationships.

developmental a., a. of the structural changes of an individual from fertilization to adulthood; includes embryology, fetology, and postnatal development.

functional a., physiologic a.

general a., the study of gross and microscopic structures as well as of the composition of the body, its tissues and fluids.

gross a., macroscopic a.; general a. studied without the use of the microscope.

macroscopic a., gross a.

microscopic a., the branch of a. in which the structure of cells, tissues, and organs is studied with the light microscope. See histology.

pathologic a., anatomical *pathology*.

physiologic a., functional a.; a. studied in its relation to function.

radiological a., the study of the body through x-ray imaging.

regional a., topographic a.; a. of certain related parts or divisions of the body.

special a., a. of certain definite organs or organ systems concerned in the performance of special functions.

surface a., the study of the configuration of the surface of the body, especially in its relation to deeper parts.

surgical a., applied a. in reference to surgical diagnosis and treatment.

topographic a., regional a.

ultrastructural a., the ultramicroscopic study of structures too small to be seen with a light microscope.

veterinary a., a. of domestic animals.

anatricrotic (an'ă-tri-krot'ik). Characterized by anatricrotism.

anatricrotism (an'ă-trik'ro-tizm) [G. *ana*, up, + *tri-*, thrice, *krotos*, beating]. The condition of the pulse manifesting itself by a triple beat on the ascending limb of the sphygmographic tracing.

anatro'pia [G. *ana*, up, + *tropē*, a turning]. Anaphoria.

obstet'ric, obstet'rical. Relating to obstetrics.

obstetrician (ob-stĕ-trish'un). A specialist in obstetrics.

obstet'rics [L. *obstetrix*, a midwife]. Tocology; the medical specialty concerned with the care of the pregnant woman during pregnancy, parturition, and the puerperium.

ob'stinate [L. *obstinātus*, determined]. **1.** Intractable (2); refractory (2); firmly adhering to one's own purpose, opinion, etc., not yielding to argument, persuasion, or entreaty. **2.** Refractory (1).

obstipation (ob-stī-pa'shun) [L. *ob*, against, + *stipo*, pp. *-atus*, to crowd]. Intestinal obstruction; severe constipation.

obstruction (ob-struk'shun) [L. *obstructio*]. Blockage or clogging as by occlusion or stenosis.

obstruent (ob'stru-ent) [L. *ob-struo*, pp. *-structus*, to build against, obstruct]. **1.** Obstructing; blocking; clogging. **2.** An agent that obstructs or prevents a normal discharge, especially a discharge from the bowels.

obtund' [L. *ob-tundo*, to beat against, blunt]. To dull or blunt, especially sensation or pain.

obturation (ob-tu-ra'shun) [see obturator]. Obstruction or occlusion.

ob'turator [L. *obturo*, pp. *-atus*, to occlude or stop up]. **1.** Any structure that occludes an opening. **2.** A prosthesis used to close an opening of the hard palate, usually a cleft palate. **3.** The stylus or removable plug used during the insertion of many tubular instruments.

obtuse (ob-tūs') [see obtund]. **1.** Dull in intellect; of slow understanding. **2.** Blunt; not acute.

obtusion (ob-tu'zhun). Dulling or deadening of sensibility.

occipital (ok-sip'ī-tal). Relating to the occiput.

occipitalization (ok'sip'ī-tal-ī-za'shun). Bony ankylosis between the atlas and occipital bone.

occipito- (ok-sip'ī-to-). Combining form for occiput, occipital.

occip'itofa'cial. Relating to the occiput and the face.

occip'itofron'tal. **1.** Relating to the occiput and the forehead. **2.** Relating to the occipital and frontal lobe of the cerebral cortex.

occip'itomen'tal. Relating to the occiput and the chin.

occiput, gen. **occip'itis** (ok'sī-put) [L.] [NA]. The back of the head.

occlude (o-klūd) [see occlusion]. **1.** To close or bring together. **2.** To inclose, as in an occluded virus.

occlusal (o-klu'zal). **1.** Pertaining to occlusion or closure. **2.** In dentistry, pertaining to the contacting surfaces of opposing occlusal units (teeth or occlusion rims), or the masticating surfaces of the posterior teeth.

occlusion (o-klu'zhun) [L. *oc-cludo*, pp. *-clusus*, to shut up]. **1.** The act of closing or the state of being closed. **2.** In chemistry, the absorption of a gas by a metal or the inclusion of one substance within another. **3.** Any contact between the incising or

masticating surfaces of the upper and lower teeth. **4.** The relationship between the occlusal surfaces of the maxillary and mandibular teeth when they are in contact.

abnormal o., an arrangement of the teeth not considered to be within the normal range of variation.

afunctional o., a malocclusion that does not permit normal function of the dentition.

balanced o., balanced articulation; the simultaneous contacting of the upper and lower teeth on the right and left and in the anterior and posterior occlusal areas in centric and eccentric positions within the functional range.

centric o., (1) the relation of opposing occlusal surfaces which provides the maximum planned contact and/or intercuspation; (2) the o. of the teeth when the mandible is in centric relation to the maxillae.

coronary o., blockage of a coronary vessel, usually by thrombosis or atheroma, and often leading to infarction of the myocardium.

eccentric o., any o. other than centric.

functional o., (1) any tooth contacts made within the functional range of the opposing teeth surfaces; (2) o. which occurs during function.

hyperfunctional o., occlusal stress of tooth or teeth exceeding normal physiologic demands.

mesial o., (1) mesio-occlusion; anterior o. (2) an o. in which the mandibular teeth articulate with the maxillary teeth in a position anterior to normal; (3) mesioclusion.

normal o., that arrangement of teeth and their supporting structure which is usually found in health and which approaches an ideal or standard arrangement.

pathogenic o., an occlusal relationship capable of producing pathologic changes in the supporting tissues.

physiologic o., o. in harmony with functions of the masticatory system.

protrusive o., o. which results when the mandible is protruded forward from centric position.

o. of the pupil, the presence of an opaque membrane closing the pupillary area.

retrusive o., a biting relationship in which the mandible is forcefully or habitually placed more distally than the patient's centric o.

traumatogenic o., traumatic o., a malocclusion capable of producing injury to the teeth and/or associated structures.

occlu'sive. Serving to close; denoting a bandage or dressing that closes a wound and excludes it from the air.

occult (ŏ-kult', ok'ult) [L. *oc-culo,* pp. *-cultus,* to cover, hide]. **1.** Hidden; concealed. **2.** Denoting a concealed hemorrhage, the blood being so changed as not to be readily recognized. **3.** In oncology, a clinically unidentified primary tumor with recognized metastases.

ochrometer (o-krom'ĕ-ter) [G. *ōchros,* pale yellow + *metron,* measure]. An instrument for determining the capillary blood pressure by compressing one of two adjacent fingers until blanching of the skin occurs, after which the force necessary to accomplish this color change is read in millimeters of mercury.

ochronosis (o-kron-o'sis) [G. *ōchros,* pale yellow + *nosos,* disease]. A pathologic condition observed in certain patients with alkaptonuria, characterized by pigmentation of cartilages and sometimes other tissues.

ochronotic (o-kron-ot'ik). Relating to or characterized by ochronosis.

oct-, octa-, octi-, octo- [G. *oktō,* L. *octo,* eight]. Combining forms meaning eight.

octan (ok'tan) [L. *octo,* eight]. Applied to fever the paroxysms of which recur every eighth day, the day of each paroxysm being included in the count.

ocular (ok'u-lar) [L. *oculus,* eye]. **1.** Ophthalmic. **2.** The eyepiece of a microscope, the lens or lenses at the upper end of a microscope by means of which the image focused by the objective is viewed.

oc'ularist [L. *oculus,* eye]. One skilled in the design, fabrication, and fitting of artificial eyes, and the making of prostheses associated with the appearance or function of the eyes.

oculi (ok'u-li) [L.]. Plural of oculus.

oculist (ok'u-list) [L. *oculus,* eye]. Ophthalmologist.

oculo- [L. *oculus,* eye]. Combining form denoting eye, ocular. See also ophthalmo-.

oculocutaneous (ok'u-lo-ku-ta'ne-us). Relating to the eyes and the skin.

oculofacial (ok'u-lo-fa'shal). Relating to the eyes and the face.

oculography (ok-u-log'răfi) [oculo- + G. *graphō,* writing]. A method of recording eye positions and eye movements.

oculogyria (ok'u-lo-ji'rĭ-ah) [oculo- + G. *gyros,* circle]. The limits of rotation of the eyeballs.

oculogyric (ok'u-lo-ji'rik). Referring to rotation of the eyeballs; characterized by oculogyria.

oc'ulomo'tor [oculo- + L. *motorius,* moving]. Relating to or causing movements of the eyeball.

oc'ulona'sal. Relating to the eyes and the nose.

oc'ulopu'pillary. Pertaining to the pupil of the eye.

oc'ulozygomat'ic. Relating to the orbit or its margin and the zygomatic bone.

oc'ulus, gen. and pl. **oc'uli (O)** [L.] [NA]. Eye; the organ of vision, consisting of the eyeball and the optic nerve.

O.D. L. *oculus dexter,* right eye; Doctor of Optometry; overdose.

-odes [G. *eidos,* form, resemblance]. Suffix denoting having the form of, like, resembling.

odont-, odonto- [G. *odous (odont-),* tooth]. Combining forms denoting a tooth or teeth.

odontalgia (o-don-tal'jĭ-ah) [odont- + G. *algos,* pain]. Toothache.

odontal'gic. Relating to or marked by odontalgia.

Saemisch's o., incision of the cornea to evacuate pus.

Scott o., a jejunoileal bypass for morbid obesity utilizing end-to-end anastomosis of the upper jejunum to the terminal ileum, with the bypassed intestine closed proximally and anastomosed distally to the colon.

stapes mobilization o., fracture of tissue immobilizing the stapes to restore hearing, especially used in patients with otosclerosis.

Stookey-Scarff o., see third *ventriculostomy.*

subcutaneous o., an o., as for the division of a tendon, performed without incising the skin other than by a minute opening made by the entering knife.

Wertheim's o., a radical o. for carcinoma of the uterus in which as much as possible of the vagina is excised and there is wide lymph node excision.

Whipple's o., pancreatoduodenectomy.

Whitehead's o., excision of hemorrhoids by two circular incisions above and below involved veins, allowing normal mucosa to be pulled down and sutured to anal skin.

Ziegler's o., a V-shaped iridotomy for the formation of an artificial pupil.

op'era'tive. **1.** Relating to, or effected by means of an operation. **2.** Active; effective.

op'erator. In genetics, operator *gene.*

opercular (o-per'ku-lar). Relating to an operculum.

operculitis (o-per'ku-li'tis) [operculum + G. *-itis,* inflammation]. Pericoronitis.

operculum, pl. **opercula** (o-per'ku-lum, -lah) [L. cover or lid]. **1.** Anything resembling a lid or cover. **2** [NA]. In anatomy, the portions of the frontal, parietal, and temporal lobes bordering the lateral sulcus and covering the insula. **3.** A bit of mucus sealing the endocervical canal of the uterus after conception has taken place. **4.** The attached flap in tear of retinal detachment. **5.** The mucosal flap partially or completely covering an unerupted tooth.

op'eron. A genetic functional unit that controls production of a messenger RNA; consists of an operator gene and two or more structural genes located in sequence in the cis position on one chromosome.

ophiasis (o-fi'ă-sis) [G. fr. *ophis,* snake]. Alopecia areata in which the loss of hair occurs in bands partially or completely encircling the head.

ophritis, ophryitis (of-ri'tis, -re-i'tis) [G. *ophrys,* eyebrow, + *-itis,* inflammation]. Dermatitis in the region of the eyebrows.

oph'ryon [G. *ophrys,* eyebrow]. The point on the midline of the forehead just above the glabella (1).

ophryosis (of-re-o'sis) [G. *ophrys,* eyebrow, + *-osis,* condition]. Spasmodic twitching of the upper portion of the orbicularis palpebrarum muscle causing a wrinkling of the eyebrow.

ophthalm-. See ophthalmo-.

ophthalmalgia (of-thal-mal'jĭ-ah) [ophthalmo- + G. *algos,* pain]. Pain in the eyeball.

partic'ulate. Relating to or occurring in the form of fine particles.

partic'ulates. Formed elements, discrete bodies, as contrasted with the surrounding liquid or semiliquid material in cells.

parturient (par-tu'rĭ-ent) [L. *parturio,* to be in labor]. Relating to or being in the process of parturition or childbirth.

parturifacient (par-tu-rĭ-fa'shent)]L. *parturio,* to be in labor, + *facio,* to make]. Oxytocic; inducing or accelerating labor.

parturiometer (par-tu-rĭ-om'e-ter) [L. *parturitio,* parturition, + G. *metron,* measure]. A device for determining the force of the uterine contractions in childbirth.

parturition (par-tu-rish'un) [L. *parturitio,* fr. *parturio,* to be in labor]. Childbirth.

parvicellular (par-vĭ-sel'u-lar) [L. *parvus,* small, + Mod. L. *cellularis,* cellular]. Relating to or composed of cells of small size.

Parvoviridae (par-vo-vĭr'ĭ-de). A family of small viruses containing single-stranded DNA; replication and assembly occur in the nucleus of infected cells. Three genera are recognized: *Parvovirus, Dependovirus,* and an officially unnamed genus that includes the adeno-associated satellite virus (unofficially named *Adenosatellovirus*).

Parvovirus (par'vo-vi-rus). A genus of viruses (family Parvoviridae), of which the Kilham rat virus is the type species, whose members replicate autonomously in suitable cells.

PAS *p*-Aminosalicylic acid; periodic acid-Schiff (stain).

PASA *p*-Aminosalicyclic acid.

pas'cal (Pa). A derived SI unit of pressure, expressed in newtons per square meter.

passive (pas'iv) [L. *passivus,* fr. *patior,* to endure]. Not active; submissive.

passivism (pas'ĭ-vizm) [see passive]. **1.** An attitude of submission. **2.** A form of sexual perversion in which the subject, usually male, is submissive to the will of his partner in sexual practices.

paste [L. *pasta*]. A soft semisolid soft enough to flow slowly and not to retain its shape.

Pasteurella (pas-tur-el'ah) [L. *Pasteur*]. A genus of aerobic to facultatively anaerobic, nonmotile bacteria (family Brucellaceae) containing small Gram-negative, rods; parasites of man and other animals. The type species is *P. multocida.*

P. multoci'da, a species that causes fowl cholera and hemorrhagic septicemia in warm-blooded animals; it is the type species of the genus *P.*

P. pes'tis, *Yersinia pestis.*

P. pseudotuberculo'sis, *Yersinia pseudotuberculosis.*

P. tularen'sis, *Francisella tularensis.*

pasteurellosis (pas'tur-ĕ-lo'sis). Infection with bacteria of the genus *Pasteurella.*

pasteurization (pas'tur-ĭ-za'shun) [L. *Pasteur*]. The heating of milk or other liquids for about 30 minutes at 68°C. (154.4°F.) whereby the living bacteria are destroyed, but the flavor or bouquet is preserved; the spores are unaffected, but are kept from developing by immediately cooling the liquid to 10°C. (50°F.) or lower.

patch. A small circumscribed area differing from the surrounding surface.

cotton-wool p.'s, cotton-wool spots; accumulations of cytoplasmic debris in the retinal nerve fiber layer caused by damage to axons.

Peyer's p.'s, *folliculi* lymphatici aggregati.

smoker's p.'s, leukoplakia.

patella, pl. **patellae** (pă-tel'ah, -tel'e) [L. a small plate, the kneecap, dim. of *patina,* a shallow disk, fr. *pateo,* to lie open] [NA]. Kneecap; the large sesamoid bone, in the combined tendon of the extensors of the leg, covering the anterior surface of the knee.

patel'lar. Relating to the patella.

patellectomy (pat'ĕ-lek'to-mĭ) [patella + G. *ektomē,* excision]. Excision of the patella.

patel'liform. Of the shape of the patella.

patency (pa'ten-sĭ). The state of being freely open or patulous.

pa'tent [L. *patens,* pres. p. of *pateo,* to lie open]. Patulous; open; exposed.

path-, patho-, -pathy [G. *pathos,* suffering, disease]. Combining forms meaning disease.

pathergasia (path-er-ga'zĭ-ah) [G. *pathos,* disease, + *ergasia,* work]. A physiologic or anatomical defect that limits normal emotional adjustment.

pathergy (path'er-jĭ) [G. *pathos,* disease, + *ergon,* work]. A term suggested to include reactions of all kinds resulting from a state of altered activity, both allergic (immune) and nonallergic.

path'finder. A filiform bougie for introduction through a narrow stricture to serve as a guide for the passage of a larger sound or catheter.

patho-. See path-.

path'oanat'omy. Anatomical *pathology.*

path'obiol'ogy. Pathology with emphasis more on the biological than on the medical aspects.

path'oclis'is [patho- + G. *klisis,* bending, proclivity]. A specific tendency toward sensitivity to special toxins; a tendency for toxins to attack certain organs.

pathogen (path'o-jen) [patho- + G. *-gen,* to produce]. Any virus, microorganism, or other substance causing disease.

pathogenesis (path'o-jen'ĕ-sis) [patho- + G. *genesis,* production]. Nosogenesis; the mode of origin or development of any disease or morbid process.

pathogen'ic, pathogenet'ic. Morbific; nosogenic; nosopoietic; causing disease.

pathogenicity (path'o-jĕ-nis'ĭ-tĭ). The condition of being pathogenic or of causing disease.

pathognomonic (pă-thog-no-mon'ik) [patho- + G. *gnōmē,* a mark, a sign]. Characteristic or indicative of a disease; denoting especially one or more typical symptoms.

thologic, pathological (path-o-log'ik, -ik-al). Pertaining to pathology; morbid; diseased; resulting from disease.

thol'ogist. A specialist pathology and practices chiefly in the laboratory as a consultant to clinical colleagues.

thology (pă-thol'o-jĭ) [patho- + G. *logos*, study, treatise]. The medical science and specialty practice concerned with all aspects of disease, but with special reference to the essential nature, causes, and development of abnormal conditions, as well as the structural and functional changes that result from the disease processes.

natomical p., pathological anatomy; the subspecialty of p. that pertains to the gross and microscopic study of organs and tissues removed for biopsy or during postmortem examination.

cellular p., (1) the interpretation of diseases in terms of cellular alterations, *i.e.*, the ways in which cells fail to maintain homeostasis; (2) sometimes used as a synonym for cytopathology.

clinical p., (1) in a strict sense, any part of the medical practice of p. as it pertains to the care of patients; (2) the subspecialty in p. concerned with the theoretical and technical aspects of laboratory technology as pertains to the diagnosis and prevention of disease.

comparative p., the p. of diseases of animals, especially in relation to human p.

oral p., the branch of dentistry concerned with the etiology, pathogenesis, and clinical, gross, and microscopic aspects of disease of oral and paraoral structures including oral soft tissues and mucous membranes, the teeth, jaws and salivary glands.

speech p., the science concerned with functional and organic speech defects and disorders.

surgical p., a field in anatomical p., concerned with examination of tissues removed from living patients for the purpose of diagnosis of disease and guidance in the care of patients.

thomimesis (path'o-mĭ-me'sis) [patho- + G. *mimesis*, imitation]. Mimicry of disease, whether intentional or unconscious.

thophysiol'ogy. Derangement or alteration of function seen in disease.

thopsychology (path-o-si-kol'o-jĭ) [patho- + psychology]. The study of deviations from normal psychological processes.

thosis [patho- + G. *-osis*, condition]. A state of disease, a diseased condition, or disease entity.

thway. 1. A collection of axons establishing a conduction route for nerve impulses from one group of nerve cells to another group or to an effector organ composed of muscle or gland cells. 2. Any sequence of chemical reactions leading from one compound to another; if taking place in living tissue, usually referred to as a **biochemical p.**

Embden-Meyerhof p., the anaerobic glycolytic p. by which glucose (most notably in muscle) is converted to lactic acid.

pentose phosphate p., Dickens shunt; a secondary p. for the oxidation of glucose, generating reducing power (NADPH) in the cytoplasm outside the mitochondria and synthesizing pentoses; does not occur in skeletal muscle.

-pathy. See path-.

patient (pa'shent) [L. *patiens*, pres. p. of *patior*, to suffer]. One who is suffering from a disease or disorder and is under treatment for it; not to be confused with "case."

patrilineal (pat-rĭ-lin'e-al) L. *pater*, father, + *linea*, line]. Related to descent through the male line.

patulous (pat'u-lus) [L. *patulus*, fr. *pateo*, to lie open]. Patent.

paucisynaptic (paw'sĭ-sĭ-nap'tik) [L. *paucus*, few, + synapse, *q.v.*]. Oligosynaptic.

pause (pawz) [G. *pausis*, cessation]. Temporary stop.

compensatory p., the p. following an extrasystole, when long enough to compensate for the prematurity of the extrasystole.

postextrasystolic p., the somewhat prolonged cycle immediately following an extrasystole.

preautomatic p., a temporary p. in cardiac activity before an automatic pacemaker escapes. See also escape.

sinus p., a spontaneous interruption in the regular sinus rhythm, the p. lasting for a period that is not an exact multiple of the sinus cycle.

Pb Lead (plumbum).

PBG Porphobilinogen.

PBI Protein-bound *iodine*.

p.c. L. *post cibum*, after meals.

PCB Polychlorinated biphenyl, an industrial carcinogen.

PCO_2, pCO_2 Partial pressure (tension) of carbon dioxide.

PCP Phencyclidine.

Pd Palladium.

p.d. Prism *diopter*.

PDLL Poorly differentiated lymphocytic *lymphoma*.

pearl. 1. A small hollow sphere of thin glass containing amyl nitrite or other fluid for inhalation; the p. is crushed in a handkerchief and its contents are inhaled. 2. One of a number of small tough masses of mucus occurring in the sputum in asthma.

epithelial p., keratin p.

Epstein's p.'s, multiple small white epithelial inclusion cycts found in the midline of the palate in most newborn infants; probably developmental in origin.

keratin p., epithelial p. or nest; a focus of central keratinization within concentric layers of abnormal squamous cells; seen in squamous cell carcinoma.

peccant (pek'ant) [L. *peccans*(*-ant-*), pres. p. of *pecco*, to sin]. Morbid; unhealthy; producing disease.

pec'ten [L. comb]. 1 [NA]. A structure with comblike processes or projections.

p. ana'lis [NA], **anal p.,** the middle third of the anal canal.

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Coronary Bypass Graft Fate: Long-Term Angiographic Study

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In 222 patients, 741 venous coronary bypass grafts were studied angiographically early, at 1 year and at a late examination at >6.5 years (mean 9.6) after operation; 565 of these grafts were also examined 5 years postoperatively. Grafts were graded for patency and disease considered to be atherosclerotic and for both extent and profile of lesions.

Graft occlusion rates increased steadily from 8% early to 20% at 5, 41% at 10 and 45% at >11.5 years after operation. All grafts were considered free of atherosclerosis early, but disease appeared in 8% at 1 year, increasing to 38% at 5 and 75% at 10 years postoperatively. Increasing involvement of vessel wall area was associated with greater protrusion of lesions into the graft lumen. Diseased grafts became more so at subsequent examinations, with occlusion occurring in many. However, absence of disease had little prognostic significance because diseased and abruptly occluded grafts were generated in those with healthy appearance at earlier examinations. For instance, 82% of very diseased grafts at the 5 year study originated from normal grafts at 1 year and 73% of occluded grafts at 1 year had appeared normal early postoperatively.

Of 590 patent grafts free of disease at 1 year, 30% were occluded at the late examination, 76% of those patent were diseased, 55% of these were diffusely diseased and 35% were >50% narrowed. Only 17% of the original 590 patent grafts were healthy at this time. Bypass graft atherosclerosis severely limits the long-term utility of these grafts. It is suggested that the solution may lie in some powerful drug regimen.

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It is well known that the long-term fate of coronary bypass vein grafts is principally determined by graft atherosclerosis. We (1) previously reported angiographic features of this disease up to 5 years after operation. We now describe its appearance and progression in coronary bypass vein grafts from 6.5 to >11.5 years postoperatively. As in our previous study, we used a grading system to define patency and atherosclerosis of 741 vein grafts studied consecutively.

Methods

Study patients and grafts. In this study, we included only those patients who had follow-up angiograms early and at 1 year and >6.5 years after operation. One hundred sixty-four patients (565 grafts) were studied early (mean 0.96 months) and at 1 year (mean 12.84 months), 5 years (mean 60 months) and >6.5 years after operation. In addition, there were 51 patients (176 grafts) studied early, at 1 year and at a remote time after operation. Two hundred thirty-seven grafts were studied at 7.5 years (mean 7.4), 403 at 10 years (mean 9.9) 61 at 12.5 years (mean 12.7) and 40 later (mean 14.2 years) after operation. Thus, 741 grafts in 222 patients were studied early, after 1 year and in the course of a late examination ≥6.5 years after operation; the majority of grafts were also examined 5 years after operation. The interval from operation to the late examination ranged from 80 to 187 months (mean 116) (9.6 years). The study included angiographic examination of 25% of all grafts in patients surviving 6.5 years after operation. The subjects were mainly military personnel, all men, ranging in age from 31 to 67 years (mean 45.7).

Operations. Preoperative and follow-up evaluation of the patients was done by the Cardio-Pulmonary Unit of the National Defence Medical Centre, Ottawa, Ontario, Canada, but operations were undertaken by five surgeons at the University of Ottawa Heart Institute, where patients usually remained for ≤48 h after operation. All operations entailing coronary bypass surgery were included in the study (for example, bypass operations also involving other procedures such as valve replacement or ventricular aneurysm repair). There were 3.3 vein grafts/operation. Internal mammary grafts were excluded. As background information, we report a perioperative mortality rate of 1.7% for all 1,202 first coronary bypass operations and of 5.4% for all 149 reoperations. In the larger group from which study patients were derived, 92.7% (824 of 889) of patients had survived 6.5 years after operation. We (2) previously reported a perioperative myocardial infarction rate of 7.8% (transmural 3.2%).

Technical background. Saphenous vein was harvested with minimal manipulation and, pending placement, was kept in normal saline solution containing 60 mg of papaver-

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Table 1. Graft Patency Grading on Follow-Up Angiography

	Early	1 Year	5 Years	7.5 Years	10 Years	>11.5 Years
Total grafts	741	741	565	237	403	101
Graft grade						
A	631 (85)	608 (82)	428 (76)	109 (46)	211 (52)	40 (40)
B	52 (7)	34 (5)	24 (4)	31 (13)	27 (7)	15 (15)
A + B (patent)	683 (92)	642 (87)	452 (80)	140 (59)	238 (59)	55 (55)
O	58 (8)	99 (13)	113 (20)	97 (41)	165 (41)	46 (45)

Numbers in parentheses are percent. A = good patency; B = graft narrowed at some point to <50% of *grafted artery*; O = graft occluded.

ine/100 ml. Most bypass grafts had a single distal anastomosis, but some were of the sequential type, our experience with these having been described elsewhere (3). Twenty-eight percent of the grafts were to the anterior descending coronary artery, 20% to its diagonal branches, 28% to branches of the marginocircumflex trunk and 24% to the trunk or branches of the right coronary artery. At angiography, grafts were selectively opacified, usually with a Judkins size 4 right coronary catheter, in at least four vertical planes ranging from 60° to the right of the mid-line to 90° to the left of the mid-line, sometimes with axial views. Catheterization was facilitated by graft loop markers placed on the aortic wall at operation. Grafts were usually demonstrated to be occluded by opacification of stumps, sometimes supplemented by collateral evidence in native selective coronary angiograms; rarely, proximal aortic-flood examinations were required. High resolution radiographic equipment was used for recording on 35 mm cinefilm at 60 frames/s.

Graft patency grading. We used the grading system previously reported (4) to define bypass graft patency. The proximal and distal anastomoses of the graft and the trunk were assessed separately and each assigned a letter: A (good), B (fair) or O (occluded). Grade B indicated stenosis *reducing the lumen to <50% of the grafted artery*. The grade for the entire graft was the lowest of the three site gradings. This was essentially a hemodynamic grading system. We used another method, previously described (1), to classify angiographic appearances we believed due to atherosclerosis. This provided more purely morphologic information. Category I indicated that the graft outline was completely smooth without any irregularity that might be due to disease; in category II grafts, <50% of the estimated surface area of the graft intima was irregular; category III grafts had >50% of the intima involved. To define this finding more precisely and perhaps add more prognostic value, we also classified the lesions into high profile or low profile types (that is, high or low rise, elevation or relief) depending on whether they *encroached >50% or <50% on what was considered to be the normal graft lumen* at that point. These grading systems, all based on the worst aspects of four-plane views, entailed use of an "eyeballing" technique. Great care was taken, however, to classify grafts as accurately as possible within the framework outlined.

Results

Graft occlusion. Graft occlusion rates early, at 1, 5, 7.5, 10 and >11.5 years after operation (Table 1) were 8%, 13%, 20%, 41%, 41% and 45%, respectively. Grafts to the marginocircumflex and right coronary arteries had a significantly lower patency rate at the late examination than did grafts to the anterior descending coronary artery and its diagonal branches (Table 2). Most of the grafts were graded A, with a small core of grade B grafts. It is of surgical importance that in the early postoperative studies, most (46 [89%] of 52) of the B gradings were assigned because of narrowing at the distal anastomosis. After 5 years, an increasing number of grade B grafts were so graded because of trunk stenosis associated with atherosclerosis.

The 7.5 year phenomenon. The striking increase in B grades at 7.5 years, followed by a decrease at 10 years, prompts an explanation applicable to other values in the 7.5 year columns of Tables 1 and 3. We (5) have drawn attention to this phenomenon elsewhere. Our ideal follow-up practice is to perform angiography early and at 1 and 5 years and then every 5 years after coronary bypass operations. Practically all our patients have early angiograms and the majority are restudied at 1 year (1,4–6), but military/civilian career, geographic and other factors reduce the number examined at 5 and 10 years after operation. Findings in a group of regularly examined, compliant and readily available patients are probably well represented in the 5 and 10 year columns of Tables 1 and 3. However, at 7.5 years (between 79 and 102 months postoperatively), we examined patients presenting for a "clinical" rather than a "routine" reason, including a number of patients who presented ostensibly "late" for their

Table 2. Vessels Grafted and Late Graft Occlusion

	Grafted (%)	Late Occlusion (%)
Left anterior descending (LAD)	28	34
Diagonal branches of LAD	20	38
Marginocircumflex	28	49
Right coronary	24	45

Right and marginocircumflex occlusion rates significantly different ($p < 0.05$) from rates in left anterior descending and diagonal grafts.

Table 3. Bypass Graft Atherosclerosis on Follow-Up Angiography

	Early	1 Year	5 Years	7.5 Years	10 Years	>11.5 Years
Patent grafts	683	642	452	140	238	55
Not diseased (I)	683 (100)	590 (92)	278 (62)	25 (18)	60 (25)	11 (20)
Diseased						
II	0	46 (7)	98 (22)	53 (38)	79 (33)	12 (22)
III	0	6 (1)	76 (16)	62 (44)	99 (42)	32 (58)
II + III	0	52 (8)	174 (38)	115 (82)	178 (75)	44 (80)
Proportion of diseased grafts high profile	0	3 (6)	24 (14)	43 (37)	62 (35)	21 (48)
Proportion of all patent grafts high profile	0	3 (0.5)	24 (5)	43 (31)	62 (26)	21 (38)

Numbers in parentheses are percent. II = graft with <50% of the intima estimated diseased; III = graft with >50% of the intima estimated diseased; high profile = atheroma encroaching >50% on graft lumen.

5 year studies but on close questioning were found to have new angina. The values in the 7.5 year column in Tables 1 and 3 are thus weighted toward more extensive graft disease and a higher rate of graft occlusion.

Graft disease. Early after operation, all grafts were considered to be free of atherosclerosis (Table 3). At 1 year, 92% of the grafts appeared smooth walled and the remainder had some irregularity of outline, involving >50% of the graft surface area in only a few cases. By 5 years, however, only 62% of grafts had normal-appearing intima and almost 50% of the remaining grafts were considered to have atherosclerosis involving >50% of the graft surface area. Five percent of the diseased grafts had high profile lesions reducing the size of the graft lumen by >50%. At 10 years, only 25% of the patent grafts were considered healthy, >50% of the diseased grafts were in category III and 35% of the diseased grafts had high profile lesions. Further deterioration was seen >11.5 years after operation. Table 3 demonstrates proliferation of the lesions we believe to be due to atherosclerosis in the plane of the vessel wall and at the same time progressively rising from the intima to obstruct blood flow. At >11.5 years after operation, the atherosclerotic process produced >50% luminal obstruction in almost 50% of the diseased grafts; at this time, slightly >50% of the grafts remained patent and 80% of these were diseased.

Diseased graft prognosis. Our data confirm that the presence of atherosclerosis in a coronary bypass vein graft presages increasing disease in the future. In 12 of the 31 instances, category II grafts in the 1 year study became category III grafts at 5 years, and 3 other grafts became occluded. Similarly, of 33 low profile lesions at the 1 year study 7 became high profile lesions at 5 years and 4 others were associated with graft occlusion. Between the 5 year study and the late examination, 55 of 98 category II grafts became category III grafts and 27 became occluded. Likewise, of 76 category III grafts at the 5 year study, 41 were occluded at the late examination. Of 150 low profile lesions at the 5 year examination, 52 became high profile and 49 showed graft occlusion at the late examination. Of 24 high profile lesions at the 5 year examination, 19 showed graft occlusion at the late examination.

Healthy graft prognosis. The absence of disease in the course of any examination did not guarantee a similar state at the next study. For instance, 62 (82%) of 76 category III grafts at the 5 year examination were category I grafts at the 1 year study. Sixty-eight (44%) of 155 category III grafts at the late examination were classified in category I at the 5 year study. Of 193 category III grafts at the late examination, 176 (91%) were classified as category I at the early study. Similarly, 30 (73%) of 41 occluded grafts at the 1 year study were classified as grade A category I grafts at the early examination and 26 (70%) of 37 occluded grafts at the 5 year study originated from grade A category I grafts at the 1 year examination. Ninety-one (53%) of 172 occluded grafts at the late examination originated from grade A category I grafts at the 1 year study.

In summary, of 590 patent grafts free of disease at the 1 year examination, 177 (30%) were occluded at the late examination; of the 413 patent grafts, 314 (76%) were diseased; 174 (55%) of the unhealthy grafts were diffusely diseased and 111 (35%) of these were >50% narrowed; only 99 (17%) of the original 590 patent grafts were healthy. Similarly, of 278 patent grafts free of disease at 5 years, 55 (20%) were occluded at the late examination, 153 (69%) of the 223 patent grafts were diseased, 69 (45%) of unhealthy grafts were diffusely diseased and 43 (28%) of these were >50% narrowed; only 70 (25%) of the original 278 patent grafts free of disease at the 5 year study were healthy at the late examination.

Discussion

Graft occlusion. Early after operation, coronary bypass grafts may become occluded by thrombus, frequently forming at the distal graft-coronary anastomosis. It is probably highly significant that 89% of our early postoperative B

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grades were assigned to grafts with distal anastomosis defects. However, these technical factors are not alone of importance. Almost 75% of grafts found occluded at the 1 year study had been angiographically normal early after operation. Intimal disruption, perhaps associated with myointimal hyperplasia, and localized platelet dysfunction may lead to the formation of an occlusive thrombus. These events are poorly understood. There is no doubt, however, that later in their course coronary bypass grafts become subject to atherosclerosis (7–15). There are proliferation of smooth muscle cells, intimal damage, the complex interaction of endothelium and locally deposited platelets and the accumulation of lipids in "foam cells" (11–13). Plaques form and assume different compositions depending on the degree of fibrosis, the extent of lipid deposit, the addition of thrombus and the occurrence of calcification. Localized aneurysm formation may take place, invariably associated with advanced atherosclerosis. The degree of disease in the bypass grafts does not appear to parallel the progress of atherosclerosis in the native coronary arteries (15). Thrombus may accumulate slowly or after an abrupt "plaque accident" similar to that occurring in a coronary artery (16). Atheroembolism may occur spontaneously or lethally at reoperation (17). The final event is graft occlusion.

Autopsy studies and examination of grafts removed at coronary bypass reoperations attest that with the passage of time atherosclerosis becomes very common in these grafts. Neitzel et al. (12) observed the disease process in 71% of grafts removed between 6 and 12 years after operation. We believe that we are observing this process at various stages in our follow-up angiograms.

Graft patency grading. Our A, B and O patency grading seems noncontroversial. The A and O grades can be assigned easily; a B grade presents some problems. Grafts are graded B because of stenosis of the proximal or distal anastomosis or in the trunk of the graft *reducing the size of the lumen to <50% of the grafted artery*. We believe that we have validated the honesty of the B grading (graft lumen <50% of the grafted artery). In a large series, we (4) demonstrated that 24% of early grade B grafts were occluded at 1 year and that 39% remained the same; however, only 6% of grade A grafts went on to occlusion and 4% became grade B ($p < 0.0005$).

Graft disease grading. Diagnosing and grading atherosclerosis in coronary bypass graft angiograms involve some speculation. We recognize that we have no systematic pathologic corroboration of our angiographic findings. Lytle et al. (10) indicated that myointimal hyperplasia and thrombus present diagnostic pitfalls. Solymoss et al. (13) described late thrombosis in vein grafts associated with nonatherosclerotic intimal hyperplasia, although this most often accompanies atherosclerosis. Nevertheless, we believe that ascription of atherosclerosis to coronary bypass graft angiograms showing what we have described as category I, II or III grafts with high or low profile lesions is in accord with pathologic and angiographic opinion (7–31). Grondin et al. (26) described these angiographic findings, including use of the terms "irregular wall," "plaque," "conventional stenosis," "spur diaphragm" and "cauliflower." These features may be seen in native vessel coronary angiograms.

In our sequential studies, as might be expected to occur with atherosclerotic disease, proliferation of lesions in the graft's mural plane is progressively associated with their elevation from the vessel wall to produce luminal obstruction. We believe that our grading system is justifiable in describing what we consider to be atherosclerosis in coronary bypass vein grafts.

Effects of drugs. For >20 years, we have given to our patients with coronary disease medications affecting the behavior of platelets for reasons arising from Duguid's encrustation theory (32) of the development of atherosclerosis. These drugs have usually been aspirin and dipyridamole, sulfinpyrazone occasionally being substituted for the former. Administration of aspirin but not dipyridamole was discontinued for 1 week before operation, sulfinpyrazone being substituted, but treatment with both aspirin and dipyridamole was started again 1 to 3 days after operation. The beneficial effect of these two agents on early and late coronary bypass graft patency has been demonstrated by Chesebro et al. (33,34). We have not had a control series. Use of these medications is not the topic of this report, but attention must nevertheless be drawn to their administration.

Graft disease and bypass grafting. An incidence of late coronary venous bypass graft atherosclerotic stenosis and occlusion generally similar to ours has been reported by others, notably in major series from the Montreal Heart Institute (8,15,31) and the Cleveland Clinic (10); our results confirm theirs. We demonstrated a relentless progression of disease in coronary bypass vein grafts with increasing large areas of intimal involvement and steady growth in the volume of lesions, graft occlusion being the end result. At 10 years after operation, 41% of our bypass grafts were occluded and 75% of those that were not occluded were diseased. Furthermore, we demonstrated in our angiograms that graft atherosclerosis behaves in a capricious manner. Bypass graft disease surely begets disease—there is nothing as atherogenic as atheroma—but a "healthy" appearance does not perpetuate itself. Graft occlusion, the final insult, is sometimes the end stage of atherosclerosis and its complications and at other times occurs for no obvious reason.

What then is the continuing long-term utility of the saphenous vein coronary bypass graft? Our limited experience with other large bore conduits, arm vein, umbilical vein and synthetic material, has been disappointing, although a single Gore-Tex right coronary bypass graft remained patent at 1 year but was occluded at 5 years after operation. Our patency rates are somewhat better for internal mammary artery grafts than for vein grafts. In a recent unpublished series of 169 consecutive internal mammary artery grafts opacified early after operation, the patency rate was 96% but there was a 10% incidence of grade B grafts, almost all

associated with distal anastomotic defects. In the long term, however, the internal mammary artery remains free of atherosclerosis and the effect of its use on late mortality has been demonstrated (35). Nevertheless, there are only two internal mammary arteries and the right vessel is anatomically limited in its reach. The right gastroepiploic artery has been used successfully for coronary bypass grafting (36,37), but its dissection complicates the coronary bypass procedure and it has not yet become widely used. Certainly, if it were not for graft atherosclerosis, the saphenous vein, which is easily accessible and plentiful, would be the ideal conduit for coronary bypass grafting.

Causes of vein graft atherosclerosis. Campeau et al. (31) demonstrated an association between elevated levels of certain blood lipoproteins and atherosclerosis in coronary bypass grafts; others (38) have narrowed the field of search. We (39) demonstrated a statistically significant relation between atherosclerosis of coronary venous bypass grafts and smoking. There are undoubtedly many other factors, ranging from intimal damage done at the time of operation to the long-term effects of "arterializing" a vein, to say nothing of possible autoimmune or even more remote genetic considerations. The reader is referred to the excellent editorial review by Grondin (11).

The future. Meticulous handling of the venous conduit at operation and exacting surgical technique are essential, particularly for early success, but these are probably not sufficient factors to prevent atherosclerosis in the long term. The high cost in lives and money of coronary bypass reoperations militates against their use in dealing with the problem of saphenous vein graft atherosclerosis. Control of conventional risk factors, particularly diet and smoking, is mandated by the available evidence. Yet this may not be enough. We have assiduously prescribed agents modifying the behavior of platelets from the beginning of our experience with coronary bypass grafting, but we doubt that our long-term results can be considered confirmation of their efficacy in preventing or retarding atherosclerosis. Perhaps our results would have been much worse if we had not used these drugs. Newer medications may save the day. These include drugs to normalize dyslipidemias (40) and the calcium channel blockers (41) reportedly used with some success. We await the advent of the agent or the technique that will restore to the saphenous vein coronary bypass graft its once great promise.

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Coronary Bypass Graft Fate and Patient Outcome: Angiographic Follow-Up of 5,065 Grafts Related to Survival and Reoperation in 1,388 Patients During 25 Years

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Objectives. We sought to examine, angiographically, the long-term fate of a large number of mainly venous coronary bypass grafts and to correlate graft patency and disease with patient survival and reoperation.

Background. Much is known about bypass graft patency and disease, but the precise relation between graft fate and patient outcome has not been substantiated and documented.

Methods. A total of 1,388 patients underwent a first coronary artery bypass graft procedure at a mean age of 48.9 years, 234 had a second bypass procedure at a mean age of 53.3 years, and 15 had a third bypass procedure at a mean age of 58.2 years during the 25-year period from 1969 to 1994. Most were male military personnel or veterans; 12% were ≤39 years old. Of 5,284 grafts placed, 91% were venous and 9% arterial. Angiograms were performed on 5,065 (98% of surviving) grafts early, on 3,993 grafts at 1 year and on 1,978 grafts at 5 years after operation; other examinations were also performed up to 22.5 years after operation, and 353 grafts were examined after ≥15 years. Grafts were graded for patency and disease. The status of all patients was known at the study's end.

Results. The perioperative mortality rate was 1.4% for an isolated first coronary bypass procedure, 6.6% for reoperation. Vein graft patency was 88% early, 81% at 1 year, 75% at 5 years and 50% at ≥15 years; when suboptimal grafts, graded B, were excluded from calculation, the proportion of excellent grafts, graded A, decreased to 40% after ≥12.5 years. After the early study, the vein graft occlusion rate was 2.1%/year. Internal mammary artery graft patency was significantly better but decreased with time. Vein graft disease appeared by 1 year and the rate accelerated by ≥2.5 years, involving 48% of grafts at 5 years and 81% at ≥15 years; 44% of the latter grafts were narrowed >50%. Survival of all patients was 93.6% at 5 years, 81.1% at 10 years, 62.1% at 15 years, 46.7% (150 patients) at 20 years and 38.4% (25 patients) at 23 years after operation. Survival decreased as age increased, but curves approximated "normal" life expectancy for older patients. Survival curves at all ages showed a steeper decline after 7 years. The rate of reoperation increased between 5 years and 10 to 14 years, then decreased to stable levels. Coronary atheroembolism from vein grafts was the major cause of morbidity and mortality associated with reoperation. Vein graft patency and disease were temporally and closely related to reoperation and survival.

Conclusions. Coronary bypass graft disease and occlusion are common after coronary artery bypass grafting and increase with time. They are major determinants of clinical prognosis, specifically measured by reoperation rate and survival. Intraoperative graft atheroembolism was a major reoperation hazard. Reoperation is definitely worthwhile but entails identifiable risks that must be dealt with.

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The fate of coronary artery bypass grafts depends on many factors, including technical faults in harvesting, handling and fashioning the conduits; thrombosis; myointimal hyperplasia; fibrosis; and a rapidly progressing variety of atherosclerosis. Nwasokwa (1) recently reviewed the extensive published data very well. The nature of our hospital permitted an attempt to correlate evolving graft morphology with clinical outcome through systematic sequential, selective, multiple plane angiographic studies. In 1978, we (2) described patency grading of 1,400 consecutive grafts early after operation and of 1,132 of these 1 year later. Subsequently, graft defects considered to be due to disease were also graded, and in 1986 we (3) reported on 1,179 vein grafts, each studied early and 1 and 5 years after operation. We (4) reported a similar study of 741 vein grafts examined in sequence >6.5 years (mean 9.6) after operation in 1991. Our principal findings were 1) Vein graft occlusion rates were ~11% early and ~50% late after operation. 2) Intimal irregularities appeared at 1 year and progressed to involve

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some 75% of grafts late after operation. 3) As disease spread over the graft surface, lesions gained bulk and protruded into the lumen, resulting in graft stenosis or occlusion. 4) Disease increased relentlessly once it appeared, but some apparently healthy grafts were unexpectedly found to be diseased or occluded in later studies.

In the present report, we describe the angiographic appearance of 5,065 assorted coronary bypass grafts (91% venous, 9% arterial), not studied in specific sequences but each examined at least once during exactly 25 years. In addition, we have correlated bypass graft fate with reoperation rates and with patient survival, demonstrating that the clinical outcome of coronary bypass grafting depends primarily on graft integrity, and we have attempted to define the relation between this determinant and its consequences.

Methods

Institutional background. Coronary artery disease is the major nontraumatic cause of serious morbidity and mortality in Canadian military personnel. Myocardial revascularization began at the National Defence Medical Centre (NDMC), Ottawa, with the Vineberg procedure (5,6) in 1965, continuing with coronary artery bypass grafting from 1969 (7). However, operations requiring cardiopulmonary bypass required brief patient transfer to cardiac surgery facilities of the Ottawa Civic Hospital, which later became the University of Ottawa Heart Institute. Nevertheless, most postoperative care and all diagnostic and follow-up activities have taken place at NDMC (8). Military medical devolution and decentralization have recently led to major institutional downsizing (9), and this determined our series' end on December 31, 1994.

Patients. There were 1,388 patients; 79% were military personnel, only 12 were women. At the first coronary artery bypass graft procedure, the patients ranged in age from 27 to 79 years (mean 48.9), at the second bypass procedure from 32 to 83 years (mean 53.3) and at the third procedure from 45 to 71 years (mean 58.2). There were 167 patients (12%) ≤39 years old; 8 of these had a second operation by this age. A previous report (10) described results of coronary artery bypass grafting in 138 patients ≤39 years old. There were 954 patients (69%) aged 40 to 54 years and only 267 (19%) ≥55 years old. Thirty-five patients had had a previous Vineberg procedure. Since 1982, 159 patients have also undergone percutaneous transluminal coronary angioplasty of one or more coronary arteries or bypass grafts, 38 before and 121 after the bypass procedure. The angioplasty procedures were performed on 103 grafts, 95 venous; on 15 (16%) of the 95 for restenosis. Three patients underwent heart transplantation; all are currently surviving, one at 10 years after transplantation. The first coronary bypass operation was performed on December 18, 1969 and the last on December 14, 1994. All operations are reported and none performed elsewhere is included. The initial patient underwent reoperation in 1977 and 1993 and is currently well.

Operations. Of the 1,637 coronary bypass procedures, 1,388 were first, 234 were second and 15 were third operations; 1,154 patients had only one bypass procedure, 219 had only two and 15 had three procedures. Fifteen percent of all operations were repeat procedures, but 17% of the patients had more than one procedure. We believe that <12 of our patients have had a repeat coronary bypass procedure elsewhere. The operations were performed by 11 surgeons; 1 performed 40% of the procedures and 4 colleagues collectively performed 54%. Normothermic anoxic cardiac arrest was used initially and cold potassium cardioplegia in the second half of the series. Coronary artery stenosis ≥50% was the indication for grafting. A total of 4,801 saphenous vein and 466 in situ internal mammary (internal thoracic) artery grafts were placed. The right gastroepiploic artery was utilized very late for six in situ grafts. There were four free internal mammary artery and three free inferior epigastric grafts. Expanded polytetrafluoroethylene conduits were used four times. Optimal use of internal mammary artery grafts was delayed; 90% of these grafts were placed after 1985 and 75% were placed at a first bypass procedure. Both internal mammary arteries were used in 12% of cases during 1985 to 1989 and in 23% of cases in the last 5 years, an important advance (11,12). Of internal mammary artery grafts, 67% were to the left anterior descending artery, 13% to its diagonal branches, 15% to marginocircumflex branches and 5% to right coronary artery branches. Adjuvant coronary endarterectomy was performed during 344 first operations and 23 reoperations; multiple endarterectomies were performed in 11% of these cases.

Complete revascularization was a constant aim. We (2) previously described 414 patients who had a mean of 3.3 grafts per primary operation before November 1976. In the present series, 3.4 grafts were placed at a first operation, 2.4 grafts at a second and 2.5 grafts at a third operation. Twenty-six percent of 5,284 grafts were to the trunk or branches of the right coronary artery, 27% were to the left anterior descending coronary artery, 19% to diagonal and 0.4% (19 cases) to septal branches and 28% to the marginocircumflex system. Proportionately fewer marginocircumflex grafts were placed at a second and fewer yet at a third operation. Most bypass grafts had a single distal anastomosis; we (13) have reported a disappointing experience with sequential grafts. Saphenous veins were harvested with minimal manipulation and held in papaverine/saline solution. *Full realization that patent but diseased vein grafts in situ pose major reoperation problems came slowly. This critically important (14) topic will be discussed later.*

Antiplatelet agents. Since 1969, we have given antiplatelet agents to all patients with coronary artery disease. Initially, we used dipyridamole and high dose aspirin, occasionally substituting sulfinpyrazone. Except in urgent cases, sulfinpyrazone, instead of aspirin, was used for 5 days before operation to decrease perioperative bleeding; the usual routine was reinstituted about 3 days postoperatively. Recently, dipyridamole has been given with aspirin only before angiography, and routine aspirin dosage is now conventional. These agents have not been evaluated formally.

Follow-up angiography. Examinations included two-plane left ventriculography and four-plane selective coronary and bypass graft angiography. Radiopaque thread rings marked aortic graft ostia. The Judkins technique was most often used, with 8F catheters (Cordis Corporation). A Judkins right coronary catheter was used for most aortic and many internal mammary artery intubations; the internal mammary artery catheter was frequently useful and the B1 (CB) catheter was sometimes invaluable. Graft occlusion was never inferred solely from difficulty in intubation; supporting coronary or aortic flood evidence was required for this determination.

We initially used meglumine diatrizoate as the contrast medium, later iopamidol. Selective vein graft angiography entails risk. We (15) previously reported coronary vein graft spasm 31 times in >10,000 selective opacifications; graft occlusion occurred in three patients, two of these sustaining nonfatal myocardial infarction. The sole death due to follow-up angiography in the present study (and in all our experience) was a result of fulminating anaphylaxis in a patient who had had four uncomplicated angiograms, also using meglumine diatrizoate, during the previous 12 years. Our mortality rate for all coronary angiography is an acceptable (16) 0.08%.

Graft angiograms and grading. Of the total of 5,284 grafts, 101 were lost to study because of perioperative death; the remaining 5,183 grafts were available for study, and 5,065 (98%) of these were examined early, 3,993 at 1 year and 1,978 at 5 years after operation. Our plan to repeat postoperative angiography every 5 years indefinitely was thwarted by lack of funds, although some patients returned repeatedly at their own expense for follow-up. Angiograms were obtained up to 22.5 years after operation. However, the number of vein grafts studied was <50 after 17.5 years, so those vein grafts examined at ≥15 years have been consolidated at 353, and internal mammary artery grafts examined at ≥5 years have been consolidated at 123. We (4) previously reported an unexpected increase in vein graft abnormality between 5 and 10 years postoperatively, "the 7.5 year phenomenon," thought to be due in part to "late" presentation of patients with covert symptoms at 5 years. Consequently, vein graft findings between principal quinquennial assessment points are assigned intermediately. Previous reports dealt with grafts that were all examined in a common temporal sequence. The present results relate to angiographic findings in *all* grafts at *all* examinations, and the number reported is thus greater.

Definitions of bypass graft patency (2) and grades of disease (3) are summarized in Table 1. All grades relate to the worst appearance in four-plane views and were visually determined subjectively. Grades, assigned by four experienced cardiologists, have been reproducible (2–4,10,13,17).

Data handling and statistical methods. Information was examined in a computerized relational data base of our own design (produced by Neodyne Consulting Limited, Ottawa, Ontario, Canada). Life table and chi-square analyses were done by standard methods (18). We knew the survival status of all patients on December 31, 1994 but have not attempted actuarial analysis by cause of death.

Table 1. Definitions of Graft Grades, Assessed by Four-Plane Angiography

Grade	Definition
Patency	
A	Excellent graft with unimpaired runoff
B	Stenosis reducing caliber of proximal or distal anastomoses or trunk to <50% *of the grafted coronary artery*. Overall graft B grade was determined by the lowest of the three specific site grades
O	Occlusion
Disease	
I	No intimal irregularity
II	Irregularity of <50% of estimated intimal surface
III	Irregularity of >50% of estimated intimal surface
HP	High profile lesion produces >50% *stenosis of graft*
LP	Low profile lesion produces <50% *stenosis of graft*

Grades A, B and O assess graft flow. Grades I, II, III, HP and LP reflect disease severity.

Results

Perioperative mortality; myocardial infarction. Perioperative mortality was defined as death from any cause during the entire stay at either hospital. Thirty-nine perioperative deaths yielded an overall mortality rate of 2.3%. However, 36 of the total group of 1,388 patients underwent coronary artery bypass grafting in association with another major cardiac procedure, such as valve replacement, and the mortality in this group was 11.1%. Excluding these 36, but including those who had coincident repair of ventricular aneurysm (6% of the remaining patients), the mortality rate was 1.4% for a first coronary bypass procedure. This rate increased to 6.6% for all reoperations, including 2 of 15 perioperative deaths for a third bypass procedure. We (10,17) have previously reported no perioperative deaths associated with a first bypass procedure in 118 patients with silent myocardial ischemia, and none in 138 patients ≤39 years old. There were no perioperative deaths for 167 first operations at ages ≤39 years in the present series.

Perioperative myocardial infarction was monitored only for reoperations. However, we (19) previously reported 56 infarctions (7.8%) complicating a first bypass procedure in 717 patients. The infarction was transmural in 23 (41%) of 56 of those patients and 2 of the 23 died; coronary endarterectomy increased the infarction rate by 170%. The incidence of infarction is probably similar for the present study.

Vein graft patency. In all, 4,801 vein grafts were fashioned and 4,592 of these were examined early, 3,706 at 1 year and 1,889 at 5 years after operation and some at other times. Table 2 lists patency grades. The patency rate was 88% early after grafting but decreased to 75% at 5 years and to 50% at ≥12.5 years. The venous graft occlusion rate was 2.1%/year after the early examination. Patency loses its cachet when grade B grafts are eliminated; grade A grafts decreased to 40% of the 580

Table 2. Vein Graft Patency Grades on Follow-Up Angiography (first, second and third operations combined)

	Early	1 Year	2.5 Years	5 Years	7.5 Years	10 Years	12.5 Years	≥15 Years
Total grafts examined	4,592	3,706	469	1,889	495	856	227	353
Graft grade								
A	3,728 (81%)	2,825 (76%)	303 (65%)	1,309 (69%)	238 (48%)	448 (52%)	90 (40%)	141 (40%)
B	299 (7%)	182 (5%)	29 (6%)	109 (6%)	60 (12%)	71 (8%)	21 (9%)	36 (10%)
A + B	4,027 (88%)	3,007 (81%)	332 (71%)	1,418 (75%)	298 (60%)	519 (60%)	111 (49%)	177 (50%)
O	565 (12%)	699 (19%)	137 (29%)	471 (25%)	197 (40%)	337 (40%)	116 (51%)	176 (50%)

Date presented are number (%) of grafts. Graft patency grades are defined in Table 1.

grafts examined at ≥12.5 years. Twelve percent of all patent grafts were graded B at ≥5 years. Early vein grafts were graded B primarily because of distal anastomotic defects, later mainly for graft trunk narrowing. At the early examination, the 8.2% incidence of B grades for marginal grafts was significantly higher ($p < 0.05$) than the 6.2% incidence rate for right, 5.8% for left anterior descending and 5.3% for diagonal vessels. This difference has been noted (2) previously, and may be due to technical difficulty with the distal anastomosis. Also confirming a previous observation (4), left anterior descending artery vein grafts were occluded early less often ($p < 0.005$) than were grafts to other vessels. This overall difference ($p < 0.05$) persisted at 1 and 5 years; even at 10 years, rates of occlusion of grafts to the left anterior descending and diagonal arteries were lower ($p < 0.05$) than for other grafts.

Arterial graft patency. Patency grades for internal mammary artery grafts are shown in Table 3. The 95% early internal mammary artery graft patency rate was better than the 88% rate for vein grafts, but 10% of the arterial grafts were grade B grafts. A learning curve effect may distort this number. During the 15 years to the end of 1984, 44 internal mammary artery grafts were examined early; 40 (91%) of these were patent and 4 (9%) were graded B. These grafts were fashioned by the most experienced surgeons. During the next 5 (learning) years 211 (93%) of 226 internal mammary artery grafts were patent, but 30 (13%) were grade B. In the 5 years to the end of 1994, 180 (97%) of 186 internal mammary artery grafts were patent, and only 11 (6%) were grade B. The B grades were usually assigned because of distal anastomotic internal mammary artery defects, but there were some lengthy trunk defects, little influenced by vasoactive drugs at angiography and perhaps due to operative trauma. Late internal mammary artery grade A grafts decreased to 77%, apparently not because of atherosclerosis. However, only 123 internal mammary artery grafts were examined late, mandating cautious interpretation of these results. Similarly, there were too few other arterial grafts for patency analysis, although five of six in situ right gastroepiploic grafts were impressively grade A and one was grade B in early selective angiograms.

Table 3. Internal Mammary Artery Graft Patency Grades on Follow-Up Angiography (first, second and third operations combined)

	Early	Intermediate	Late
Total grafts examined	456	320	123
Graft grade			
A	386 (85%)	267 (83%)	94 (77%)
B	45 (10%)	24 (8%)	4 (3)
A + B	431 (95%)	291 (91%)	98 (80%)
O	25 (5%)	29 (9%)	25 (20%)

Data presented are number (%) of grafts. Because of the smaller number of internal mammary artery grafts, the grouping of follow-up data points differs from that used for vein graft patency in Table 2. Early = up to 6 months; Intermediate = 1 year and 2.5 years; Late = ≥5 years. Graft patency grades are defined in Table 1.

Vein graft disease and fate. Atherosclerosis is rare in native internal mammary arteries (20) and was not found in internal mammary artery grafts. However, Table 4 shows intimal abnormalities appearing in vein grafts 1 year after operation and steadily increasing, until 239 (83%) of 288 patent grafts were diseased at ≥12.5 years. Curve B in Figure 1 reveals the suddenness of attack of vein graft disease after 2.5 postoperative years, and Table 4 shows that the incidence of the more extensive grade III disease outstrips that of grade II disease after 5 years. Furthermore, high profile lesions (producing stenosis ≥50%) were present in 106 (44%) of 239 diseased grafts and 37% of all *patent* grafts at ≥12.5 years, the steady increase with time seen in curve C of Figure 1. Increasing lesion bulk clearly complicated extension of disease in the mural plane. The interrelation of vein graft patency, disease and occlusion, the last two rising together in curves A and B of Figure 1, is obvious, as is the inexorable wastage of nondiseased patent grafts in curve D. The message is malign and powerful.

Survival after a first coronary bypass procedure. The survival data on all 1,388 patients after the first coronary artery bypass graft procedure, is shown in Table 5 and curve A of Figure 2. At 10 years, the proportion surviving was 81%, at 15 years 62%, at 20 years 47% and at 23 years 38% (25 survivors). The curve declines gradually to ~7 years postoperatively, with a steeper decline thereafter. The data are classified by age into the three panels of Figure 3, based on data in Table 5. All curve slopes increase at 5 to 7 years postoperatively. Survival times of patients ≤39 years old are better than those of older patients, particularly at ages ≥55 years. The panels display population life expectancy curves for comparable Canadian men (21). Survival data for subjects ≤39 years old are also plotted against comparable data reported by Gertler et al. (22) in a 1964, 15-year follow-up study of 91 medically managed patients <40 years old.

Table 4. Vein Bypass Graft Disease on Follow-Up Angiography (first, second and third operations combined)

	Early	1 Year	2.5 Years	5 Years	7.5 Years	10 Years	12.5 Years	≥15 Years
Patent grafts	4,027	3,007	332	1,418	298	519	111	177
Not diseased (I)	4,027 (100%)	2,812 (94%)	284 (86%)	731 (52%)	87 (29%)	119 (23%)	16 (14%)	33 (19%)
Diseased								
II	0	138 (5%)	32 (10%)	372 (26%)	82 (28%)	178 (34%)	30 (27%)	45 (25%)
III	0	57 (2%)	16 (5%)	315 (22%)	129 (43%)	222 (43%)	65 (59%)	99 (56%)
II + III	0	195 (7%)	48 (14%)	687 (48%)	211 (71%)	400 (77%)	95 (86%)	144 (81%)
High profile lesions								
Proportion of diseased grafts	0	19 (10%)	6 (13%)	291 (42%)	71 (34%)	125 (31%)	43 (45%)	63 (44%)
Proportion of patent grafts	0	19 (0.6%)	6 (2%)	291 (21%)	71 (24%)	125 (24%)	43 (39%)	63 (36%)

Data presented are number (%) of grafts. Disease grades are defined in Table 1.

Survival after reoperation. At 10 and 15 years after operation, the survival rate was 72% and 57%, respectively, for a repeat operation (curve B, Fig. 4), compared with 81% and 62%, respectively, for all operations (curve A, Fig. 2). Figure 4 shows the survival curves after the most recent bypass procedure of patients having only a primary procedure and of those having a reoperation. Early differences relate to perioperative mortality, but later disparities are slight, especially at >10 years. However, Figure 5 reveals the significant value of reoperation, when survival from the first bypass procedure, rather than from the last operation, is considered.

Indications for reoperation. Stable and unstable angina were equally represented in the groups with a first and a repeat bypass procedure. However, the incidence of unstable angina doubled before the second procedure and affected all 15 patients before the third procedure. Some 20% of patients did not have angina before either their first or second bypass procedure. In a previous series (17) of 723 consecutive operations, the incidence of asymptomatic patients was 16%. Differences between those asymptomatic patients and patients with angina, including differences in long-term survival (23), were insignificant. Angiographic indications for reoperation in the present study were bypass graft failure in 80% of cases, failure combined with new native coronary disease in 12% and progression of native artery disease alone in 8%. Old grafts were occluded in 51% of cases. An ascending order of occlusion rate was seen in left anterior descending (41%), diagonal (46%), right (52%) and marginocircumflex (60%) coronary artery grafts. Fifty percent of patent grafts were healthy; disease was extensive (grade III) in 69% of the other 50%. High profile lesions (>50% graft stenosis) were seen in 51% of the grade II (moderate disease) grafts and in 67% of grade III (severe disease) grafts.

Timing of reoperation and morbidity and mortality. The cumulative incidence of reoperation appears in curve D, Figure 2. The actual annual rate of reoperation (not displayed) increased significantly 5 years after the first coronary bypass procedure, plateaued at 10 to 14 years and then decreased to a lower but steady level. However, a repeat operation was performed in 31 patients within 6 months of the first bypass procedure, in 40 patients within 12 months and in 53 patients

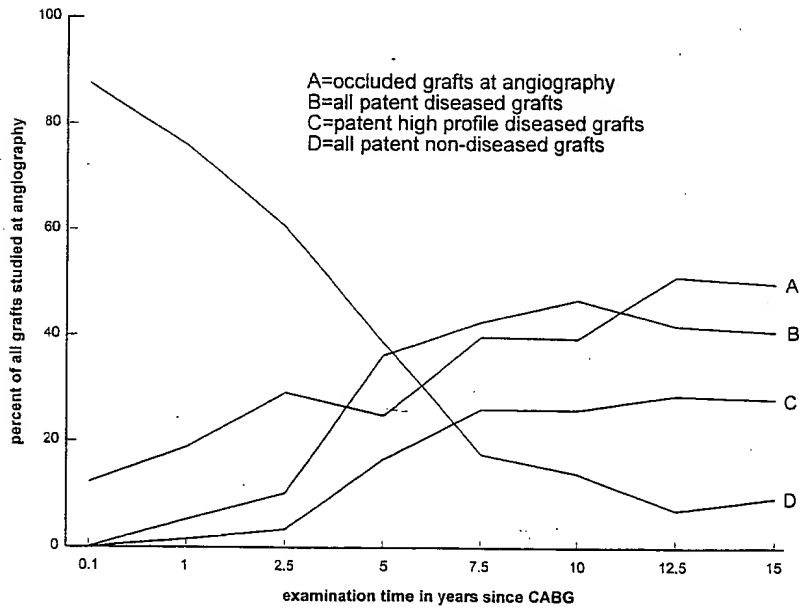

Figure 1. Vein graft disease and occlusion. The graft occlusion rate was 2.1%/year after the first postoperative study. All categories of graft disease are included. High profile disease produces >50% graft stenosis. Note the increasing disease attack rate after 2.5 years. CABG = coronary artery bypass grafting.

Table 5. Survival After a First Coronary Artery Bypass Procedure Compared With That in the Series of Rahimtoola et al. (54) and in the Coronary Artery Surgery Study (CASS) (55)

	5 Years		10 Years		15 Years		20 Years		23 Years	
	No.	Survival	No.	Survival	No.	Survival	No.	Survival	No.	Survival
Present series: 1,388 patients (99% *men*, mean age 48.9 years)	1,226	93.6%	928	81.1%	556	62.1%	150	46.7%	25	38.4%
Age group										
≤39 years	154	95%	129	85%	86	68%	36	55%		
40 to 54 years	872	95%	693	84%	411	64%	98	46%		
≥55 years	200	85%	106	68%	9	47%	1	30%		
Rahimtoola et al.: late cohort, 1974 to 1988 (5,468 *men*, mean age of total cohort [7,026] 61.1 ± 9.9 years)		89%		74%		56%	(5)*	(38%)*		
CASS 1974 to 1979 (6,922 *men*, mean age 54.6 ± 8.5 years)	6,096	89%	4,921	73%	272	52%				

*Twenty-year value for entire 1969 to 1988 *gender-unspecified* cohort. Data presented are number of patients and survival rate.

within 24 months. There were no (0%), one (2.5%) and two (3.8%) perioperative deaths in each of these groups, respectively. The early operations were mainly in the first years of the series. The perioperative mortality rate was 7.1% for reoperations after 24 months, but it was 11.8% (10 of 85) for those performed >10 years after the first operation.

The presence of diseased but patent grafts, particularly those with high profile lesions (>50% graft stenosis), increased reoperation morbidity and mortality. The incidence of myocardial infarction and perioperative death in patients with healthy or occluded grafts, or both, was insignificantly different from that in patients undergoing a first bypass procedure. However, the incidence increased fivefold in patients who underwent reoperation with one or more diseased patent grafts. Only 1 of 16 deaths related to reoperation was of noncardiac origin (pancreatitis with splenic vein erosion). However, 9 (60%) of 15 cardiac deaths were due to proved or strongly suspected intraoperative coronary atheroembolism. The latter was previously demonstrated (24) angiographically in a survivor of reoperation. In our patients who had a myocardial infarction, there was a highly significant correlation between graft disease with high profile lesions and atheroembolism. Eight of nine patients with a fatal infarction had grade III disease and all nine had high profile lesions. Twenty-one percent of myocardial infarctions that occurred at reoperation were fatal. Predictably, mortality rose with the interval between operations, correlating with the rising incidence of patent but diseased grafts. Perioperative deaths tripled as the interoperative interval increased from <5 years to 5 to 10 years and rose fourfold after 10 years.

Graft status after reoperation. All grafts in survivors of the bypass procedure were studied early. Of 406 vein grafts, 78%

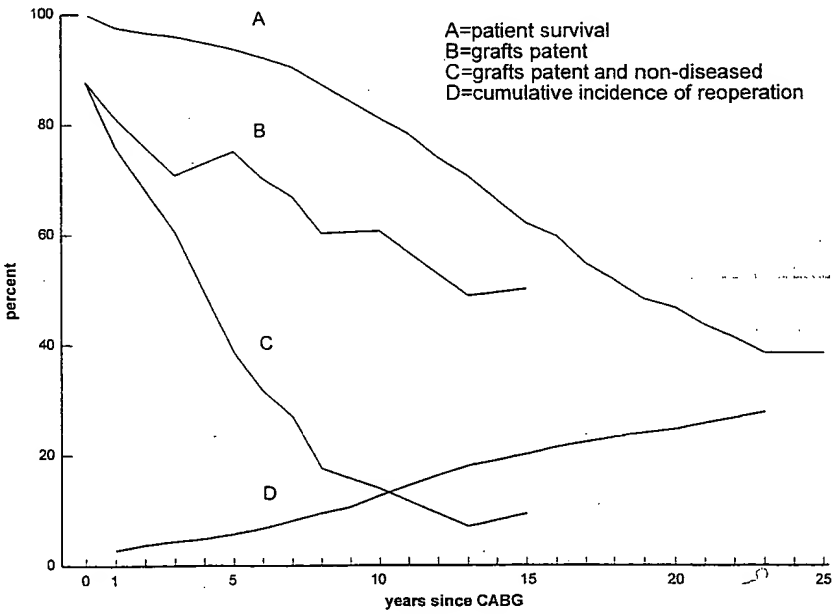

Figure 2. Survival of all 1,388 patients after a first coronary artery bypass graft procedure, reoperations and graft fate. Standard actuarial methods were used to construct reoperation curve D, as for the survival curve A. Perioperative deaths are included. Note the change in the slope of curve A at ~7 years. This figure summarizes the study's findings.

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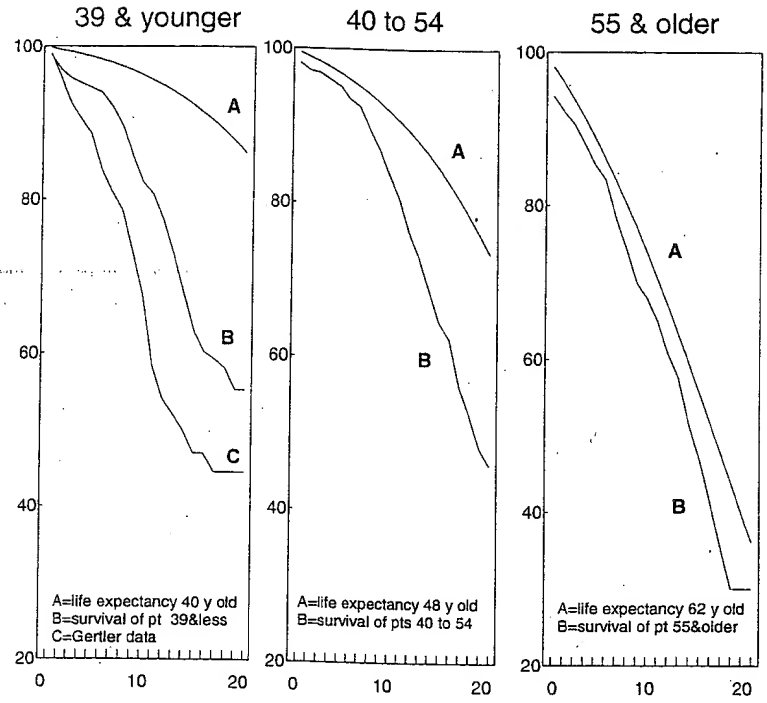

Figure 3. Age-related survival after coronary artery bypass grafting. Data in present study (curve B) compared with age-matched life expectancy for Canadian men (21) (curve A) and with that of young men with coronary disease treated medically before 1964 described by Gertler et al. (22) (curve C). Note the change in curve B slopes at 5 to 7 years. pt = patient.

were grade A, 6% grade B (84% patent) and 16% were occluded. Of 111 internal mammary artery grafts, 81% were grade A, 12% grade B (93% patent) and 7% were occluded.

Graft fate and patient outcome. The interrelation between coronary bypass graft disease and occlusion, on the one hand, and reoperation and patient survival, on the other, is displayed in Figure 2, which summarizes the salient findings of this study.

Discussion

The 1978 editorial comment (25) that "graft occlusion is uncommon and most patients who do well do not undergo post-operative coronary angiography," was promptly challenged by the angiographic description (2) of a large number of consecutive coronary bypass grafts, with occlusion rates of 11% early and 19% at 1 year after operation. The graft occlusion rate in the present study was 12% for 4,592 saphenous vein grafts and 5% for 456 internal mammary artery grafts early after operation, rising to 51% for vein grafts after 12.5 years and 20% at late internal mammary artery examinations. This is a considerable problem.

Bypass graft disease. Perioperative occlusion of bypass grafts may be due to thrombosis resulting from localized platelet dysfunction at the site of intimal damage, but it is later associated with atherosclerosis (14,26–37). Although pathologic changes are similar in both, venous bypass graft disease does not parallel in severity atherosclerotic progression in native vessels (14), as accelerated vein graft atherosclerosis is characterized by instability and the fragility of late lesions. Intimal damage is followed by smooth muscle proliferation, a

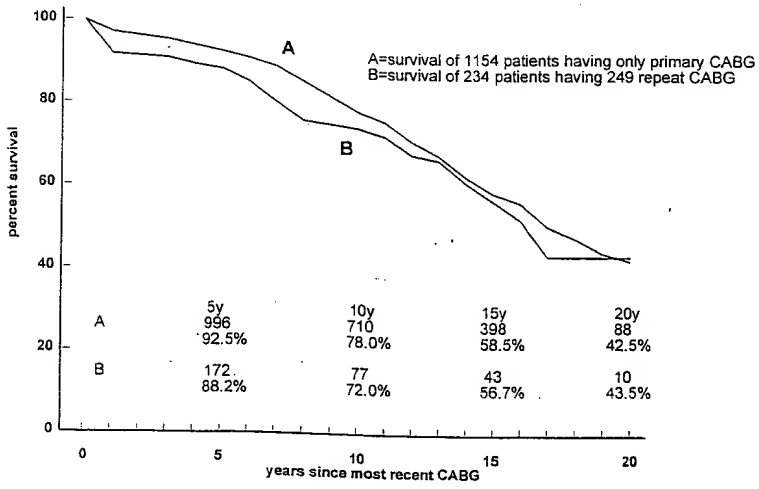

Figure 4. Survival after repeat (B) versus primary (A) coronary artery bypass grafting (CABG). Perioperative deaths are included. Survival times are from the most recent procedure. Year, number of survivors and percent survivors are listed.

complex interaction between endothelium and platelets, the presence of lipids in "foam cells," and the appearance of plaques, that differ in character by degree of fibrosis, lipid deposition, thrombosis and, occasionally, late calcification. Late thrombosis may occur (38) in vein grafts with nonatherosclerotic intimal hyperplasia, but it is uncommon. Thrombus forms slowly or suddenly after a "plaque accident" (plaque rupture) (39,40) in a coronary artery or bypass graft (41,42). Atheroembolism occurs spontaneously or with cardiovascular manipulation at reoperation (36,43), leading to coronary occlusion (24), often lethal. Results of graft biopsies and autopsy studies attest to the frequency of atherosclerosis in older grafts; lesions have been noted (34) in 71% of grafts examined 6 to 12 years postoperatively.

Early angiographic findings are problematic. Myointimal hyperplasia and thrombus may present diagnostic difficulties (26). Our attribution of atherosclerosis to vein graft irregularities seen 1 year after operation (4) has been questioned (27), and the condition has been ascribed to localized myointimal hyperplasia. Nevertheless, vein graft atherosclerosis before 1 year has been described histologically (30,31). However, high profile defects were seen at 1 year in only 0.5% of patent grafts in an earlier series (4) and in 0.6% of patent grafts in the present study. We have chosen to use consistent criteria to interpret angiographic findings, which are similar at earlier and later times. We believe that attribution to atherosclerosis of changes observed in sequential angiograms accords with general pathologic and angiographic opinion. Grondin et al. (44) have provided excellent descriptive terms, including "irregular wall," "plaque," "conventional stenosis," "spur diaphragm" and "cauliflower". Sequential study pictures of "low profile" disease, which proliferates in the mural plane, evolving to heaped up "high profile" obstructive lesions, similar to the angiographic atherosclerotic progression in native coronary arteries, have supplemented these observations.

A 1974 Montreal Heart Institute report (45) noted presciently that "the attrition rate [of these grafts] may be progressive. Therefore, it is imperative to obtain long-term angiographic follow-up in patients with coronary vein grafts. Such studies may help determine the fate of the saphenous vein in the aorto-coronary position. . . ." These words highlight the extensive studies in this field from other centers, particularly the work done in Cleveland, Montreal and Houston (14,33,35–38,43–53). Our projects have differed only in focus, and the results are in accord with and complement those of others.

Bypass graft fate. Our internal mammary artery grafts did better than vein grafts in the short term (patency rate 95% vs. 88%) but less well in the long term, when the proportion of grade A internal mammary artery grafts decreased from 85% early to 77% late. The striking decrease in grade B grafts from 10% early to 3% late, coincided with the increase to an occlusion rate of 20% at ≥5 years. However, the limited long-term data in Table 3 may not justify didactic conclusions.

A technical defect, usually at the distal anastomosis, is probably the most important factor in perioperative bypass

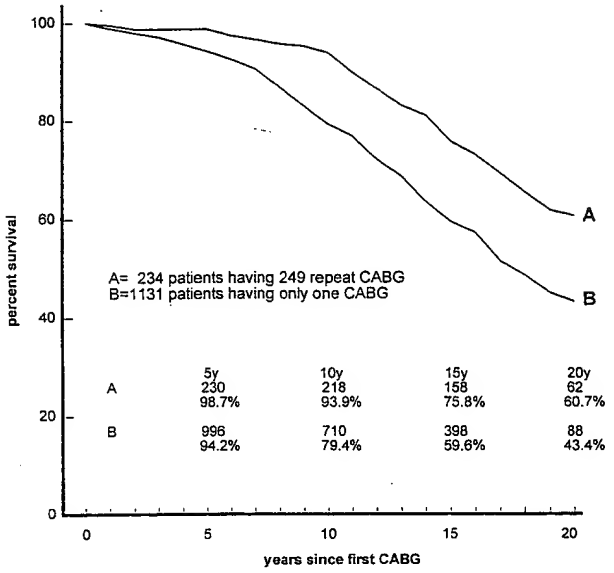

Figure 5. Overall survival of patients having more than one coronary artery bypass graft procedure. This graph includes all patients surviving the first bypass procedure and compares the *overall survival from the first bypass procedure* of the 234 patients (group A) who had a later reoperation, with that of the 1,131 patients (group B) who had only one bypass procedure. Those who died perioperatively at the first bypass procedure are excluded, because they were not at risk for reoperation. Reoperation mortality appears in the curve for group A at the approximate times that might be expected from reoperation times, noted in the text. It appears that overall survival from the time of the first bypass procedure is enhanced in patients (group A) undergoing reoperation.

graft occlusion. B graft grades were assigned (2–4) early after operation in 80% to 90% of cases because of distal defects. Our previously reported 1-year occlusion rate for grade B grafts (2) was 24% compared with 6% for grade A grafts, so grading is prognostically potent. Later vein graft occlusion reflects developing graft atherosclerosis, but it may occur unexpectedly (3,4). Five years after operation, 50% of the patent vein grafts were diseased; this rate increased to 83% at ≥12.5 years, with almost 50% of the lesions producing >50% graft stenosis.

Survival. Our survival data are displayed in Figures 2 to 5. Comparison with results reported (53–55) in other long-term studies is hindered by differences in patient age and other disparities. For instance, only 6.3% of the patients of Rahimtoola et al. (54) were ≤44 years old; whereas 12% in our series were ≤39 years old, with a wider discrepancy at later ages. Nevertheless, allowing for study differences but taking account of gender, our survival rates appear superior; Table 5 compares our results with those from Portland, Oregon (54) and a recent Coronary Artery Surgery Study (55) series. Figure 3 attests that our young surgically treated patients fared better at every stage than did those in the study of Gertler et al. (22) in the era before coronary artery bypass grafting. The closer approximation of patient and general population survival curves with increasing age is striking in Figure 3. Paradoxically,

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survival time after bypass grafting is longer for younger than for older patients, but the latter gain life expectancies closer to the "normal" for their ages; however, this is surely a multifactorial phenomenon. There may also be several reasons for the apparently significant benefit of reoperation, surprisingly revealed in Figure 5. This phenomenon was shown in Figure 13 of Lawrie et al. (53) but was not discussed. Perhaps unknown preselection factors favor those patients who survive to reoperation.

Reoperation. Seventeen percent of our patients had one or more reoperations. The cumulative incidence (Fig. 2), is smaller than in some series, perhaps because of longstanding efforts to achieve optimal myocardial revascularization (3.3 grafts/patient undergoing a first bypass procedure before 1977). High rates of reoperation in the first 2 years after a first bypass procedure during our early experience were due to concern for maximal planned surgical benefit, which persuaded us to reoperate frequently for essentially angiographic indications. Some reoperations might well have been delayed. Happily, except for 2 of 53 patients, both with major clinical problems, no patient died who underwent reoperation before 24 months. Lack of coronary angioplasty was another incentive for reoperation; 83% of 40 reoperations within 12 months of a first bypass procedure were done before angioplasty was available to us.

The perioperative mortality rate five times greater for repeat than for primary operations is a matter of grave concern. We recognize the high risk of myocardial infarction and death due to coronary atheroembolism (36,56,57) at reoperation and know that minimizing these events requires meticulous surgical technique illuminated by precise information on graft status. The handling and disposition of old grafts at reoperation (49,57) is a topic of inestimable importance. Loop et al. (49) have reported reducing the perioperative mortality rate to <3%, and this is an admirable therapeutic goal.

Care of the bypass graft. Because first causes are as yet unalterable, optimal control of risk factors for atherogenesis must be ensured. Smoking is a major problem. We (58) reported that men continuing to smoke after coronary artery bypass grafting had a significantly greater disposition to graft atherosclerosis and occlusion than did nonsmokers; 67% of those patients smoked before operation and only 50% had stopped smoking 5 years later. Voors et al. (59) have clearly demonstrated the clinical consequences. The smoking habit is hard to curb. Of 138 military patients ≤39 years old who underwent coronary artery bypass grafting (10), 88%, or twice the proportion in the Canadian Armed Forces study (60), smoked before operation and only slightly <50% had stopped 5 years later. Control of dyslipidemia may be better, because new drugs have changed the odds significantly. Scandinavian Simvastatin Survival Study (61), Pravastatin Limitation of Atherosclerosis in the Coronary Arteries I (62) and West of Scotland Coronary Prevention Study Group (63) (pravastatin) studies herald a major therapeutic advance. However, optimal utilization of therapy may be the greater challenge (64,65). With respect to other drugs, we have given agents affecting platelet behavior to all patients undergoing coronary surgery since 1969 but have not done a systematic study. Conventional long-term anticoagulant therapy in patients with inoperable graft disease seems to have been useful, and we believe that this treatment option deserves its present attention. Finally, we are certain that a dedicated follow-up program of risk factor control and early detection of complications is invaluable. Unfortunately, the necessary resources are increasingly hard to find.

The conduit. Internal mammary artery grafts, particularly from both the left and the right artery together, have come into common use quite slowly, but they improve survival (12,66–68). The right gastroepiploic artery (69,70) will probably also prove to be a valuable long-lasting conduit. Our experience with 109 right gastroepiploic artery Vineberg implants (7) and a very few, but splendid, bypass grafts has been excellent. We are dubious about the inferior epigastric artery and cannot comment on the radial arteries as conduits. Synthetic conduits have not proved themselves in any hands. Perhaps a superb new fabric awaits discovery, but this seems unlikely. The supply of arteries is limited and vein grafts will be with us for a long time yet.

Technicalities. Shiley Incorporated (71) recently warned that the identity of the person welding outlet struts to valve flanges was a "new" risk factor for prosthetic cardiac valve failure. Concern for the human variable, led us, in 1983, to examine the early patency rates of 424 coronary bypass grafts fashioned by five senior surgeons during 1981 to 1982. There was no significant difference in overall graft patency for the five surgeons, but there were surprising internal variations. The most striking was a grade O (occlusion) graft incidence rate of 17% (16 of 94) juxtaposed with a 1% incidence rate of B grades for Surgeon X, when the incidence rate of B grades for his four colleagues was 5% to 7% (20 of 330). Furthermore, Surgeon X had 88% to 92% A ratings for right, left anterior descending and marginocircumflex artery grafts, but there were 9 occlusions (56%) without any B grades, in 16 grafts to diagonal vessels. These branches are fairly accessible and usually less important than the parent trunk. We concluded that some differences in operative results probably occurred because of the heavy responsibility for surgical residency training in a teaching hospital. This is a problematic topic, especially in a time of surgical "report cards" (72,73), and it may need to be addressed formally.

The bottom line. A quarter-century of efforts in our institution to alleviate coronary stenosis with coronary artery bypass grafting have yielded morbidity, mortality and increased life expectancy results at least as good as those reported by others. However, all the early promise of coronary bypass grafting has not been fulfilled, and an insidiously deadly variety of atherosclerosis progressively chokes most vein grafts and, in the end, extinguishes their benefit. The clinical consequences are evident. Arterial grafts offer better results but have limited potential. Many difficult problems in coronary bypass grafting remain to be addressed. They include optimal timing of intervention, selection of the best conduits, methods of ensuring technical excellence, control of disease risk factors, moni-

toring of long-term graft integrity, prompt detection of those requiring reoperation and, not least, methods of ensuring that reoperation be as safe as possible.

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Aortic Anastomotic Devices Adverse Event Report Analysis

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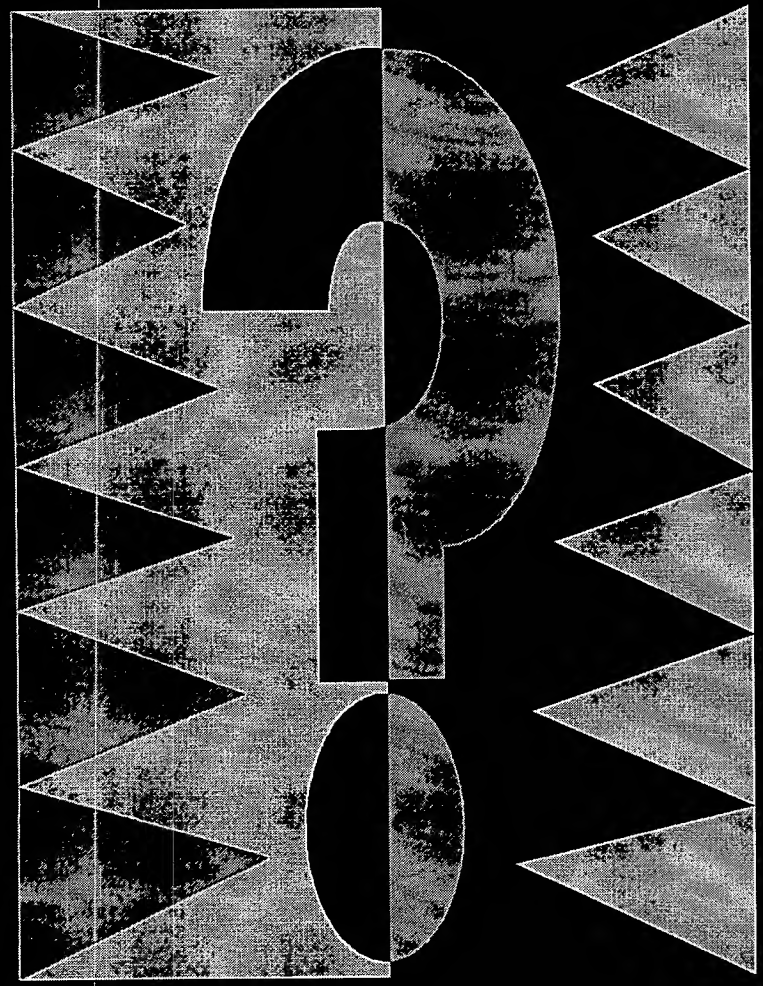
Outline

- FDA's Medical Device Reporting System (MDR)
  - description
  - limitations
- Search methodology
- Findings
- Conclusions
- Considerations
- Questions for panel

MDR – A Brief Description



- Nationwide passive surveillance
- Mandatory and voluntary reporting
- Types of reports

Limitations of MDR

- Underreporting
- No incidence data
- Biased reporting
- Uncertain causality

Methodology for Data Retrieval

- Product code
- May 24, 2001 - March 1, 2004

Overall Counts

- TOTAL REPORTS 213
  - 2001 - 11
  - 2002 - 53
  - 2003 - 145
  - 2004 - 4
- DEATH 23
- INJURY 185
- MALFUNCTION 5

Patient Characteristics

- Age 35 – 83 years
- Gender
  - Male 52%
  - Female 24%
  - Unspecified 24%
- Event Location
  - Domestic 81%
  - Foreign 7%
  - Unspecified 12%

DEATHS
N= 23

- Time of occurrence: within 18 days
- Problems
  - Occlusion / Thrombus 12*
  - Aortic Dissection 7*
  - Device Detachment 6*

*One report with both dissection + detachment

* One report with both thrombus + detachment

Death report: Example

A patient was implanted with an aortic anastomotic device during an off- pump procedure. No difficulties were encountered with loading or deployment of the device. Recovery was good for 40 hours when the patient suddenly lost consciousness after a dramatic drop in blood pressure. CPR was initiated and blood appeared in the drains. At re-operation, the aortic connector was detached from the aorta and the patient died after 10 minutes. The autopsy revealed the cause of death was hemorrhagic shock.

INJURIES

N= 185

- Most frequently reported patient problems
  - **STENOSIS** **82**
  - **OCCLUSION/THROMBUS** **60**

- Time of occurrence (days): stenosis/occlusion
  - Within 30 9
  - >30 to 90 9
  - >90 to 180 10
  - >150 to 279 2

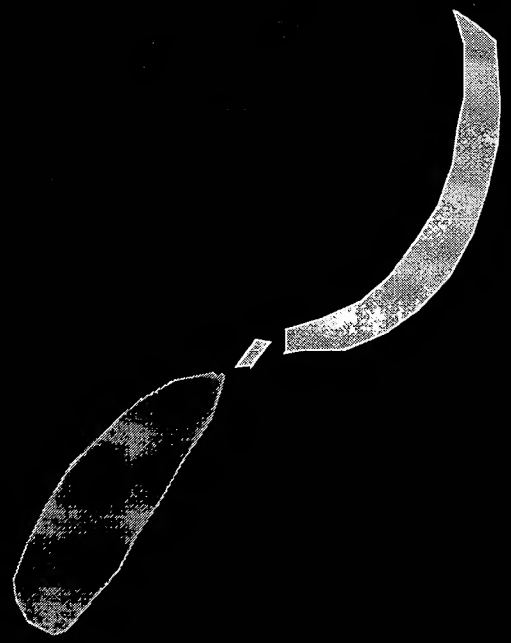
MALFUNCTIONS
N= 5

Anchor tip closed (1)

Aortic plug not seen (2)

Aortic laceration (1)

Connector failure (1)



CONCLUSIONS

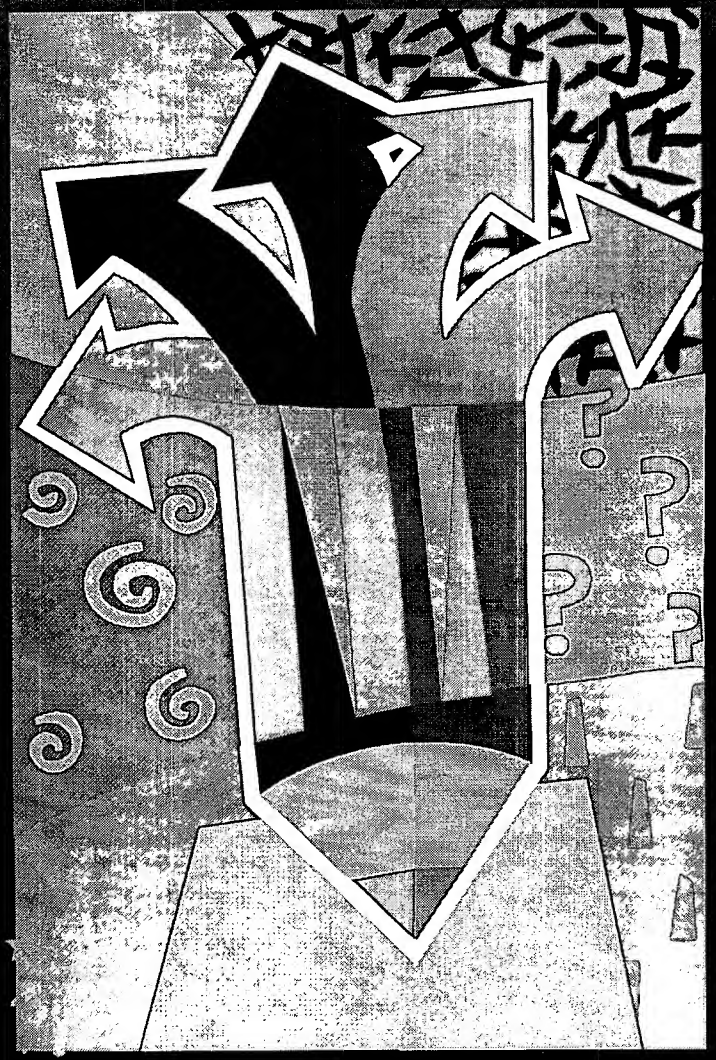
- Reports of SERIOUS OUTCOMES
- Reports suggest DEVICE-RELATED occurrences
- Reported events reflect SHORT-TERM experience

Considerations

- Failure analyses of adverse events
- Risk/benefit data

Questions for panel consideration

- Is long-term failure rate data collection necessary?
- Should studies comparing patient outcomes between those with standard suturing vs. sutureless anastomotic devices be done?
- Is further study of device-related events needed?



Vascular Anastamotic Devices for CABG

- Dina Fleischer, Branch Chief, Circulatory Support and Prosthetics Devices Branch
- Kachi Enyinna, Scientific Reviewer, Circulatory Support and Prosthetics Devices Branch
- Wolf Sapirstein, MD, Medical Officer

A Clinical Imperative

Scope of Problem

- 350,000-500000 procedures per year
- 2.5 CABG per patient

Modification to CABG Procedure

- Venous Conduits
  - CASS
  - Induced Ventricular Fibrillation
  - Hypothermic anoxic arrest
  - Cardioplegic arrest
- Arterial Conduits
- Minimal Access Direct CABG (MIDCAB)
- Beating Heart CABG (BH and OPCAB)

CABG Morbidity

- Median Sternotomy
  - Incisional Trauma -> MIDCAB
- Cardiopulmonary Bypass
  - Inflammatory/Immunologic→BHCAB OPCAB
- Neuro-cognitive Complications.
  - Extracorporeal Circulation (OPCAB)
  - Aortic Manipulation (ITA; T-grafts)
- Anastamotic Devices as Morbidity Prophylactic

CABG Patency

- Autogenous Venous Grafts
  - 5% failure peri-operative
  - 10-15% at 1 year
  - 1-4% per year → 50% at 10years
- Internal Thoracic Grafts
  - 95-98% peri-operative patency
  - 90-95% 1 year patency

CABG Failure Attribution of Cause

- Peri-operative:
  - Technical construction
  - Inadequate run-off
  - Inadequate conduit
- 6 month - one year
  - Neo-intima hyperplasia
  - Native CAD progression
- Continuum from 6 months
  - CAD (Native and Conduit vessel)

Anastamotic Devices Benefits

- Standardized anastamosis
- Rapidity of construction
- Avoidance of aortic clamping
- Diminished manipulative trauma to vessels
- ?Conduit protection from injury
- Facilitates OPCAB, MIDCAB, BHCAB

Anastamotic Devices Disadvantages

- Compliance mismatch
- Material promotes local thrombus and inflammation.
- Conduit and/or vessel trauma by device deployment
- Flawed design of anastamosis prejudicial to laminar flow
- Revision unfriendly

Assessment Problems

- CABG failure multifactorial
- Instruments
  - Invasive
  - Non-invasive (Stress Echo/EKG:MRI: Spiral CT:EBT)
- Observational vs Experimental Study
- Control: Randomized vs Concurrent RCT
- Duration of Study

Variables Confounding Study Design

- Multi-factorial causes CABG failure
- Proximal vs Distal Anastamosis Devices
- Vein vs Arterial Conduit
- Differences in Anastamosis devices' Design

Study Template

- Randomized
- BHCAB vs CABG
- Stratified:
  - Vein conduit
  - Arterial Conduit
  - Aortic vs Distal
- Similarity vs Superiority Trial:
  - LCL 5%
  - 95% patency LIMA @ 9 months
  - 90% patency Vein @ 9 months
- Sample Size

QUESTIONS FOR PANEL

Vascular Anastomosis Devices for CABG Panel Meeting March 18, 2004

Trial Design

1. Please comment on the choice of control in the clinical trial required to evaluate vascular anastomosis devices for CABG. The gold standard of sutured CABG anastamoses has a well documented history of over thirty years:

Trial Design

a. Can historical data from sutured CABG anastomosis device trials be used as the control in the device studies?

Trial Design

b. Alternatively, are concurrently performed CABG controls necessary given the multi-factorial causes of CABG failure, e.g. technical construction, extent and progression of native vessel disease, condition of conduit and progression of intima hyperplastic and atheromatous degeneration, and the introduction of drugs for mitigation of arteriosclerotic disease (CAD)?

Trial Design

c. If these trial designs are inadequate, should randomized controlled clinical trials be performed?

Trial Design

2. With regard to device placement and device design, please address the following:

    a. Given the considerable differences between the proximal and distal CABG anastomoses, what, if any, differences in study criteria should be required?

Trial Design

b. Are there certain aspects of the clinical study design (e.g. length of follow-up, endpoints) that should be required for all devices irrespective of device form and function? For example, the U-clip performance closely duplicates that of a suture, whereas the Symmetry has greater similarity to a stent.

c. It is rarely possible to determine the cause of conduit failure. Can you suggest criteria to determine whether a failure is device related?

Trial Design

3. Do you believe that the significant differences between an arterial conduit and a venous conduit warrant distinct study criteria and assessment for each? If so, please identify these criteria and analyses.

Trial Design

4. Should the primary effectiveness endpoint be graft patency alone, or include both graft patency and myocardial perfusion?

Endpoint Evaluation

5. With regard to appropriate patient follow-up:

   a. In view of the possible persisting risk of failure of some mechanical anastomosis sites, distinct from progression of native vessel disease, what duration of follow-up is advisable for pre-market evaluation?

Endpoint Evaluation

b. Should post-market follow-up be required to assess long term device effectiveness? If so, please define the appropriate length of follow-up after primary patency evaluation.

Endpoint Evaluation

6. Can non-invasive measuring instruments, e.g., echocardiography, ultrafast spiral CT, MRA, EBT, etc., be used for primary assessment of graft patency or is angiographic follow-up necessary? And at what time points should patency be assessed?

Surgery For Coronary Artery Disease

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In the four decades since the first surgical coronary revascularization procedures were performed, dramatic advancements have been made on multiple fronts in the understanding and treatment of coronary artery disease. These advances range from the study of atherosclerosis, where we now know that this is a dynamic, multifactorial process, to the most recent developments in percutaneous and surgical revascularization. Large studies from the 1970's, comparing medical and surgical therapy, helped define which groups of patients benefited from coronary artery bypass grafting (CABG). In general, those patients with left main disease, and patients with significant two- and three- vessel disease with depressed ventricular function were found to have improved long term survival with surgery. Further studies indicated that use of the left internal mammary artery (LIMA) to the left anterior descending (LAD) artery, as well as obtaining complete revascularization, significantly impacted on long term survival. The introduction of percutaneous transluminal coronary angioplasty (PTCA) and stenting have led to a dramatic increase in the number of percutaneous coronary interventions (PCI) performed, from 32,300 in 1983 to 400,000 in 1995.

The increased number of PCI's has had a significant impact on the patient population undergoing surgical revascularization. Edwards et al[1], analyzing The Society of Thoracic Surgeons National Database of patients receiving CABG between 1980 and 1990, found an increase in the mean age from 58 to 64 years, a higher proportion of women, more reoperations, worsening ventricular function, and an increased number of emergent and urgent operations. Simply put, patients undergoing coronary surgery are "sicker" than ever before. This is of significant concern because operative risk for CABG is largely determined by patient age, comorbid conditions, reoperation, and emergent status. Poor ventricular function remains important, although less ominous than in the past. With improvement in perioperative management, including myocardial protection, the overall mortality for isolated CABG remains at approximately 3%, despite the increasingly complex patient population.

Some of the major themes in recent years in the surgical treatment of coronary artery disease have been the use of multiple arterial conduits, minimally invasive bypass surgery, and the use of transmyocardial laser for patients with angina who are not revascularization candidates. This article will provide an update on these specific developments for the surgical treatment of ischemic heart disease.

Arterial Conduits

The most important determinant of late outcome is the type of bypass conduit used. Loop et al[2], in a sentinel article in 1986, found that the use of the left internal mammary artery (LIMA) in grafting the left anterior descending artery (LAD) had a significantly positive impact on long term survival. In fact, the LIMA - LAD graft is a more important predictor of survival than progressive coronary artery disease. In addition, lower hospital mortality is associated with mammary artery grafting. The success of the LIMA as a conduit is thought to be due to release of endothelium-derived nitric oxide and prostacyclin, which inhibit smooth muscle proliferation and atherosclerosis, thus promoting graft longevity. These reports led to an increased use of mammary artery grafting, such that in 1997, ~80% of patients undergoing first time bypass surgery received a single mammary artery. Most commonly,

CABG is performed by grafting the LIMA to the LAD, and using saphenous vein grafts (SVG) to the other obstructed arteries. At 10 years, the patency rate of the LIMA is ~90%, and that of SVG is ~50%.

Given that a LIMA - LAD graft prolongs survival and reduces cardiac events, and that saphenous vein conduits perform less well, surgeons became interested in using additional arterial conduits to reduce the rate of reoperation and to enhance long term survival. The most logical choice was the right internal mammary artery (RIMA). In comparing bilateral vs. single mammary artery patients, Lytle et al[3] reported that bilateral mammary grafting had decreased risks of reoperation and late mortality. Patients with moderate to severe ventricular dysfunction who had bilateral mammary grafting had a significantly lower reintervention rates, although no benefit on survival was demonstrated. However, Sergeant et al[4], in a series of 9600 patients, reported that the return of angina and survival after CABG were not influenced by use of multiple arterial grafts. Concern about sternal wound infection, especially in diabetic and obese patients, as well as the patency and technical issues in using the RIMA, have limited its use. In 1997, only about 8% of patients received bilateral mammary grafts.

Aside from the mammary artery, the most widely used arterial conduit for CABG is the radial artery. Introduced in 1970's, the radial artery graft was rapidly found to be unsatisfactory, with extremely poor patency rates. This was thought to be due to arterial spasm. Renewed interest in the radial occurred with the discovery of a few patients from the 1970's who were found to have patent radial artery grafts 20 years postoperatively. With further study, improved harvesting techniques, and antispasmodic medications, the radial artery was reintroduced in the1990's, and the results have improved markedly. The patency rate for radial artery grafts has been encouraging, 92% at 1 year and 84% at 5 years. Thus, the radial artery has gained widespread acceptance as the second choice for arterial grafting after the mammary artery.

Prior to radial artery harvest, it is mandatory to assess adequacy of ulnar collateral circulation to the hand. Acute hand ischemia is an extremely rare event when assessment of collateral circulation is done. The most common complication after radial harvest is dysesthesia of the arm and hand (8-10%), which usually resolves.

Additional arterial conduits include the gastroepiploic and inferior epigastric arteries. Generally, these conduits are used only if there is a need for additional conduits, as these are technically more difficult and spasm remains a concern.

The bulk of medical evidence indicates that the use of the LIMA- LAD is a critical component for long term survival. Additional arterial conduits are most useful in younger patients, as this group is most likely to benefit from the decreased rate of cardiac events and reoperation, and from the potential for enhanced survival. Multiple arterial conduits are also useful in patients who have inadequate saphenous veins or lower extremity ischemia. Further long-term studies are needed to accurately assess the proper role of these conduits.

Minimally Invasive Cardiac Surgery

During the past decade, the medical and lay press has given a great deal of attention to all types of "minimally invasive" or "minimal access" surgery, especially beating heart surgery. Introduced in the 1960's, beating heart surgery never gained widespread acceptance in this country, due to further developments and refinements in cardiopulmonary bypass as well as myocardial protection. The performance of a microsurgical anastomosis in a motionless heart became the gold standard operation for bypass surgery with resultant low mortality, documented graft patency, and superior patient

survival.

In recent years, there has been renewed interest in beating heart surgery, mainly based on the avoidance of the potentially deleterious effects of cardiopulmonary bypass. It is well known that bypass initiates a series of physiologic derangements including activation of systemic inflammatory response, which can affect many end organs. Elderly patients, as well as those with severe lung, kidney, and cerebrovascular disease, have increased complication rates when placed on cardiopulmonary bypass. It was mainly for those reasons, as well as for patients with isolated left anterior descending disease, that minimally invasive bypass surgery had appeal and was `rediscovered' in the United States. Beating heart surgery had been widely used for more than 20 years, mostly in South America, with very good results. Initial acceptance of beating heart surgery in this country was limited due to concern over the ability to correctly perform the critical left internal mammary to left anterior descending anastomosis on a beating heart, as well as the difficulty of performing a complete revascularization.

The term minimally invasive coronary bypass surgery is difficult to define. Is it the surgical approach, i.e. length of the incision, or is it the avoidance of cardiopulmonary bypass, or both? The International Society for Minimally Invasive Cardiac Surgery defines four approaches:

1. Minimally Invasive Direct Coronary Artery Bypass (MIDCAB): This procedure is done on a beating heart through a small anterior thoracotomy. In general, it only offers access to the left anterior descending and diagonal coronary arteries. It is not widely used due to limited exposure, difficulty in harvesting the mammary artery, and the applicability to patients with only single vessel disease, which generally represents <5% of surgical cases. Furthermore, the pain from thoracotomy may be greater than from sternotomy.
2. Off Pump Coronary Artery Bypass (OPCAB): By far, this is the most commonly used approach. The procedure is performed by conventional median sternotomy, which permits harvest of the internal mammary artery and access to all coronary arteries.
3. Port-Access CABG: In this procedure, the bypass grafting is performed through small incisions, but with conventional cardiopulmonary bypass. The connections to the heart-lung machine are made through the femoral vessels rather that through the open chest. This approach is time consuming, technically difficult, and poses risk to patients with lower extremity arterial or venous insufficiency. It has not been widely applied.
4. Robotic Coronary Artery Bypass: With this technique, instruments are introduced through small incisions in the chest and manipulated by robotic arms controlled by the surgeon, who is seated at a computer console. The use of robotic coronary endoscopic surgery is in the initial stage of development. Early results are positive and the development of complete multi-vessel endoscopic CABG is on the horizon.

With the improvement in stabilization devices which hold the coronary arteries nearly motionless while the heart continues to beat, there has been a dramatic increase in the number of OPCAB's performed. It is estimated that in 1999-2000, 25-30% of all coronary bypass operations were OPCAB's, up from 5% in 1996-1997. Contraindications to OPCAB include cardiogenic shock and persistent hemodynamic instability during the manipulation of the heart required to expose the coronary arteries. Other relative contraindications depend on surgeon comfort and experience, and include patients with obesity, cardiomegaly, need for lateral wall revascularization, and pectus excavatum. Those patients with coronary arteries that are small, intramyocardial, or calcified remain a challenge. It is generally agreed that the quality of the revascularization should not be sacrificed for the sake of a minimally invasive procedure.

There is a wealth of data claiming equivalent if not superior results of OPCAB over conventional

CABG. One of the difficulties in interpreting this data is that there is no prospective, randomized trial comparing the two approaches. Furthermore, patient selection varies widely. Conventional bypass is considered the gold standard, with well established long term graft patency rates and survival. Recent published studies of OPCAB patients by centers with large experience show very good early graft patency rates. Puskas et al[5], reported a 98.8% overall graft patency rate, and 100% for mammary grafts, in 167 patients studied after OPCAB. In general, the majority of published studies now show at least equivalent early graft patency rates as compared to conventional CABG. Concern about the completeness of revascularization remains, as most studies show that patients in the OPCAB groups receive fewer grafts. More recent reports indicate that increasing surgical experience and improved coronary stabilizers allow complete revascularization of all obstructed arteries.[5]

Overall morbidity and mortality rates vary in the literature, but complications such as reoperation for bleeding, stroke, atrial fibrillation, mediastinitis, renal failure, myocardial infarction, and death do not consistently differ between OPCAB and conventional CABG patients. Arom et al[6], in a retrospective study comparing the two groups, found significantly decreased mortality rate with OPCAB in the highest risk group of patients. Interestingly, this paper also points out with one year follow up there was a trend toward increased recurring angina and interventional procedures in the OPCAB group. Whether due to anastomotic difficulties or incompleteness of revascularization, this remains an obvious concern.

Most studies comparing the two groups show that OPCAB patients are extubated earlier, have reduced blood transfusion requirements, shorter intensive care unit stay, shorter hospital stay, and lower overall cost. However, Bull et al[7], found no significant difference in hospital stay or costs between groups. Potential reductions should be interpreted in light of the fact that OPCAB patients tend to receive fewer grafts than conventional CABG patients do.

An important issue which has received much public attention in recent years is cognitive impairment following cardiopulmonary bypass. Diegeler et al[8] showed postoperative cognitive impairment in 90% of patients undergoing conventional CABG and no impairment in the OPCAB group. This suggests that cognitive impairment is strongly associated with cardiopulmonary bypass, possibly due to microemboli, and that avoidance of bypass might reduce neuropsychologic impairment following CABG.

The goal of minimally invasive coronary bypass surgery is to achieve a complete revascularization with less pain and shorter length of stay with patient safety and long-term outcome that is identical to (or better than) conventional CABG. Patient care should not be compromised in a rush to perform the latest procedure. While the early results of beating heart surgery are encouraging, more study of these surgical procedures is needed.

Transmyocardial Laser Revascularization (TMR)

In addition to improving long-term survival, one of the most important benefits of complete revascularization is relief of angina. As many as 6 million Americans suffer from angina. With appropriate risk modification, medical therapy, and, when necessary, percutaneous and surgical revascularization, the vast majority of patients improve. However, there are patients who continue to have severe refractory angina despite maximal medical therapy, and whose coronary disease in not amenable to revascularization. For this group of patients, treatment options have traditionally been limited, with refractory angina continuing to frustrate both patient and physician.

In recent years, there has been extensive study of transmyocardial laser revascularization (TMR). In this procedure, a laser is used to create transmural channels from the epicardium to the endocardial surface of the left ventricular wall, thereby allowing perfusion of the ischemic myocardium with oxygenated ventricular blood. The two most commonly used lasers, the CO2 and the holmium:YAG, use thermal ablation to create transmyocardial channels. It is now generally accepted that the success of this procedure, i.e. the relief of angina, is not due to patency of these channels, as most studies show occlusion of the channels with necrotic debris within a few weeks after the procedure.

Leading theories of the mechanism of TMR in the relief of angina include stimulation of angiogenesis and myocardial neural ablation. The myocardial injury and inflammation caused by TMR have been shown to elevate the levels of certain angiogenic growth factors, causing angiogenesis and neovascularization. However, most studies do not demonstrate a consistent increase in regional myocardial blood flow or ejection fraction after TMR, although there have been reports of improvement in regional wall motion during dobutamine stress testing[9]. Denervation of the ischemic myocardium has also been proposed as a mechanism for the effect seen with TMR[10]. It is possible that more than one mechanism may be responsible for the anti-anginal effect.

Currently patients with medically refractory Class III/IV angina who are not candidates for CABG or percutaneous revascularization, may be candidates for TMR. Clinical trials demonstrate a consistent improvement in angina in patients with refractory Canadian Class III and IV angina, who are not candidates for traditional revascularization procedures. Two large studies, by Frazier[11] and Allen[12], found significant improvements in angina and quality of life at one year, compared to medical therapy. Angina had improved by at least two Canadian Classes in > 70% of TMR patients. However these, and other studies have failed to demonstrate a significant survival benefit with TMR, and DeCarlo et al[13] found a significant return of angina with longer follow up. Therefore, while initial clinical trials are encouraging, further study of TMR is needed, especially in the areas of sustained angina relief and long term survival.

TMR is being increasingly applied in combination with CABG, with TMR being performed in those regions where bypass grafting is not feasible. An additional exciting area of study is direct administration of angiogenic growth factors as well as gene therapy in conjunction with TMR.

Summary

1. Patients undergoing coronary revascularization today are "sicker" than in the past.
2. Use of multiple arterial conduits during coronary revascularization may lead to fewer reinterventions and prolonged survival.
3. Beating heart surgery has shown excellent early graft patency rates, and the ability to achieve complete revascularization is increasing with surgeon experience.
4. In the short term, TMR significantly improves angina in >70% patients who are not candidates for percutaneous or surgical revascularization.

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Coronary Artery Bypass Grafting for Multi-Vessel Coronary Disease on the Beating Heart: Comparative Study of 500 Patients

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Key words:
Beating heart surgery, coronary artery bypass grafting.

Introduction: We present the mid-term results of coronary artery bypass grafting for multi-vessel disease on the beating heart in comparison to conventional surgery with the use of cardiopulmonary bypass.

Methods: We studied a total of 500 patients over a period of 14 months. Group A (on-pump) consisted of 240 pts, whereas Group B (off-pump) consisted of 260 pts. The following parameters were investigated: mortality, incidence of acute myocardial infarction and stroke at day 30, intubation time, blood transfusions, biochemical markers and the duration of hospitalization.

Results: There was a significant difference in the incidence of stroke, as well as in the increase of serum creatinine between group A and B (3% vs. 0% and 1 ± 0.4 vs. 0.9 ± 0.3 respectively). Patients operated on the beating heart had less need of inotropic support (62% in group A vs. 17% in group B), less transfusions (88% vs. 58%), spent less time in the Intensive Care Unit (2.21 days vs. 2) and in the Hospital (6.97 vs. 5.93).

Conclusions: Coronary artery bypass grafting on the beating heart is safer than on-pump surgery. Off-pump surgery is associated with fewer post-operative complications and quicker mobilization of patients when compared with conventional surgery.

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The development of cardiac surgery in the last 30 years is directly related to the improvement of the techniques of Cardio-Pulmonary Bypass (CPB). However, CPB utilization constitutes one of the primary causes of perioperative complications[1]. These complications relate to hypoperfusion, cardioplegia administration with the potential of inefficient maintenance of left ventricular contractility and mainly to the interruption of normal blood flow to the aorta, with potential complications to the brain and the kidneys[2-5]. In an attempt to avoid the above-mentioned complications, there was recently a renewal of interest in the performance of Coronary Artery Bypass Grafting (CABG) without using CPB ("off-pump"), i.e. on the beating heart[6-8]. This technique, although was performed for the first time in the early days of coronary artery bypass surgery in the 60s, remained out of use in the following decades due to the development of the CPB and the use of cardioplegia. Certain important studies in recent years, however, have focused on this old technique[9] again. However, the access to deep areas that have to be revascularized remains problematic, as does the possibility of complete revascularization of the heart using arterial grafts. In this study, we present the mid-term results of CABG on patients with multi-vessel coronary artery disease (≥2 vessels) on the beating heart, in comparison to the results of "on pump" surgery. For this purpose, a comparative analysis was carried out on

various clinical and laboratory parameters of the patients during the first 30 postoperative days. The operations were carried out at our Institute during the last two years and, in a significant percentage of patients, the operation was performed with the use of a new technique of complete revascularization with arterial grafts only[10].

Material and methods

Patients and inclusion criteria

The study covers a period of 14 months (January 1999 - March 2000). During this period, CABG surgery was performed on 500 patients. During the first 6 months of the study, all patients were operated on with the use of CPB and administration of intermittent warm blood cardioplegia (Group A, n = 240). In the following 8 months of the study, all patients were operated off-pump on the beating heart (Group B, n = 260) and they represent 90% of the total number of patients operated on for coronary artery disease during the second period. Apart from the standard inclusion criteria for revascularization on the beating heart (appropriate coronary anatomy and coexistent pathological conditions that potentially increase mobility and mortality following the use of CPB)[11,12], we have extended such criteria to include a) older patients (>70 years old), b) patients with atheromatous aorta, c) reoperations and d) patients with severely depressed left ventricular function (ejection fraction <30%). Exclusion criteria initially included the presence of extensive atheromatous disease of the coronary vessels, moderate degree of aortic or mitral valve insufficiency and tachyarrythmias. Then, all patients that participated in the study had a CABG on the beating heart, regardless of the coronary anatomy.

Method of Anesthesia

The anesthesia protocol applied was the same for all patients. Following the placement of the patient on the operating table with a heating blanket underneath at 37°C and with preheated gel pillows, induction to anesthesia was performed with the administration of bolus Midazolam 10-15mg and a maintenance dose of 0.1-0.3mg/Kg/h. Fentanyl was administered in a bolus intravenous dose 7.5-15μg/Kg and supplemented accordingly during the operation. Neuromuscular block was accomplished with the administration of Pancuronium bromide 0.1-0.15mg/Kg and continuous ventilation was maintained at a ratio of air/ oxygen 30:70. Heparin was intravenously administered at a dose of 100 IU/Kg to achieve an ACT between 290 to 340. Rotating the operating table to Trendelenburg position helped in certain cases (anastomosis of the circumflex artery) to maintain hemodynamic parameters.

Surgical Technique

For Group A, the operations were performed through a median sternotomy using intermittent hyperkalemic and hypermagnesemic warm blood cardioplegia according to an established protocol[12]. The temperature of the patient during CPB was maintained at 34°C.

The revascularization technique of the circumflex coronary artery system (Figure 1) that we applied and we have already published,[13] was the following: the operating table was placed at a 20° Trendlenburg position and was rotated as much as possible to the right, towards the surgeon. Two folded umbilical tapes (2cm wide and 80cm long) were sutured with 0 silk suture, one at the border between the posterior and septal pericardium and the other at the level of the left upper pulmonary vein between the phrenic nerve and the midline. One of the ends of each tape was used to raise the posterior pericardium as much as possible and then it was fixed on the surgical field towards the assistant's side. In this way, the apex of the heart was turned to the midline and upwards. A mechanical stabilizer (Abbey Surgical, Surrey, UK) fixed directly to the sternal dilator

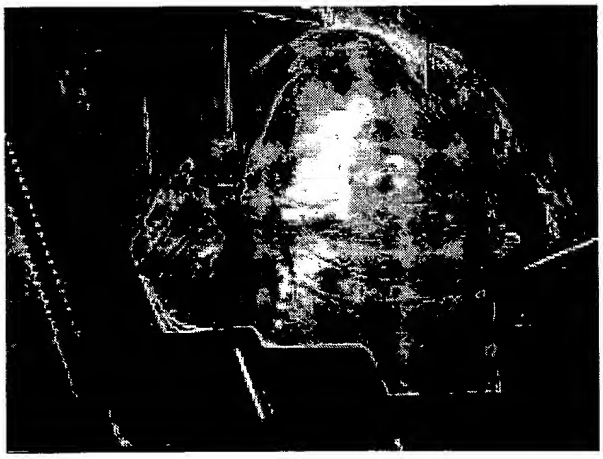

Figure 1. Revascularisation of the circumflex artery with the aid of a stabiliser.

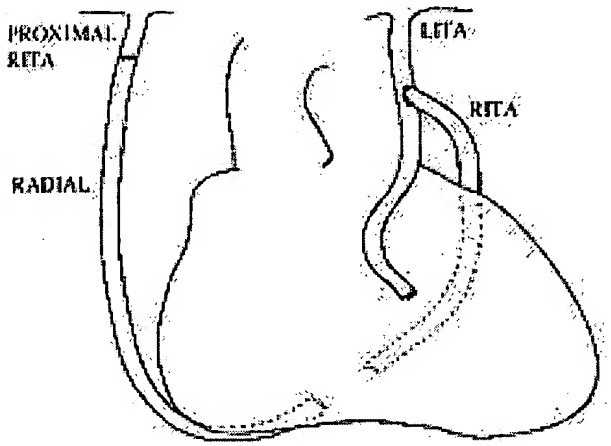

Figure 2. Schematic presentation of the technique of total revascularisation with the use of arterial grafts.
RITA: right internal thoracic artery.
LITA: left internal thoracic artery.

was used to support the heart in this position and to reduce the movement of the area in which the anastomosis was to be performed. Then, the arteriotomy was performed without using coronary snares. Instead, we introduced intraluminal shunts of appropriate size with the help of a carbon dioxide blower/humidifier. Anastomosis was performed in the usual fashion and the shunts were removed before tying the sutures.

In a significant percentage of patients, complete revascularization of the heart was accomplished with the use of arterial grafts only. One of the techniques used has been published in the past[10] and is shown schematically in figure 2.

Clinical and Biochemical Parameters

The main objectives of the study were to evaluate the mortality during the first 30 post-operative days as well as the in-hospital morbidity. In order to comparatively evaluate the morbidity of both methods, several clinical parameters were analyzed, a) the intubation time, b) the administration of inotropic drugs, c) the amount of blood transfusions, d) the incidence of acute perioperative myocardial infraction (MI) and e) the incidence of stroke. The postoperative diagnosis of MI was based on the presence of two out of three standard criteria: a) increase of the creatine kinase myocardial fraction (CK-MB) value by more than 30% of the total value of CK, and b) development of a new pathological Q-wave. The development of a local or atypical precordium pain was not considered an MI criterion. The biochemical markers that were included in the analysis were a) creatinine kinase myocardial fraction (CK-MB) value, and b) serum creatinine value (Cr). During the intensive care unit (ICU) stay, blood and plasma transfusions, intubation time and hospitalization days both in ICU and in the hospital in total, were also studied.

Statistical analysis

The data is presented as a mean value ± standard deviation (mean ± SD). The values were compared using Student's t-test and the qualitative characteristics were compared using a chi-square test. Comparisons between the two groups were made in the basic clinical characteristics such as gender, age, number of diseased vessels and left ventricular ejection fraction. A limit of statistical significance was considered the value of 5% ($p < 0.05$).

Results

Table 1 shows the basic clinical characteristics of the two groups. There were no differences between the two groups as regards gender, age, severity of the coronary artery disease, ejection fraction and preoperative biochemical parameters. The total number of grafts used in Groups A and B was 2.7 ± 0.4 and 2.6 ± 0.5 respectively, while the number of arterial grafts was 1.6 ± 0.5 and 1.7 ± 0.8 respectively, hence such differences were not statistically significant.

Table 2 summarizes the results regarding the main objectives of the study. There were no significant statistical differences in mortality at 30 days, or the time of acute MI incidence between the two

Table 1. Characteristics of patients.

	CPB CABG Group A (n=240)	OP CABG Group B (n=260)	p value
Men	205 (85%)	210 (80%)	NS
Age	63,7±7,9	64,0±10,1	NS
Unstable angina	148 (62%)	166 (64%)	NS
Ejection fraction			
Good (EF > 50%)	165 (69%)	170 (65%)	NS
Moderate (EF 30% - 50%)	60 (25%)	75 (29%)	NS

CPB CABG = cardiopulmonary bypass coronary artery bypass surgery
OP CABG = off pump coronary artery bypass surgery
EF = ejection fraction.

Table 2. Clinical and laboratory parameters of patients during and after surgery.

	CPB CABG Group A (n=240)	OP CABG Group B (n=260)	p value
Inotropic	148 (62%)	45 (17%)	< 0,0001
CK-MB	37 ± 78	18 ± 23	< 0,0001
Serum Creatinine	1 ± 0.4	0,9 ± 0,3	< 0,009
AMI	6 (2,5%)	3 (1,1%)	NS
Stroke	7 (3%)	0	< 0,03
30-day mortality	5 (2%)	1 (0,4%)	NS

CPB CABG = cardiopulmonary bypass coronary artery bypass surgery
OP CABG = off pump coronary artery bypass surgery.

groups. Significant differences were observed in the biochemical markers of the study, such as the increase of CK-MB and serum creatinine levels. A significant clinical finding was the absence of strokes in Group A and less inotrope utilization than Group B patients.

During the stay in the intensive care unit (ICU), intubation time and blood and plasma transfusion requirements were less for Group B patients (Table 3). Finally, both the stay in the ICU and the stay in the hospital were significantly reduced for Group B patients.

For 55% of the patients, total arterial revascularization was achieved using arterial grafts only. Figure 3 illustrates radial artery anastomosis at the right

Table 3. Comparison of parameters during treatment in the Intensive Care Unit.

	CPB CABG Group A (n=240)	OP CABG Group B (n=260)	p value
Intubation time (hours)	9,96 ± 6,48	6,10 ± 2,3	< 0,01
Erythrocytes transfusions (units)	1,13 ± 1,28	0,13 ± 0,35	< 0,001
Plasma transfusions (units)	1,1 ± 1,68	0,07 ± 0,37	< 0,01
Patients without transfusion	51 (22%)	110 (42%)	< 0,01
Treatment in ICU (days)	2,21 ± 0,41	2,00 ± 0,00	<0,01
Hospitalization days	6,97 ± 1,92	5,93 ± 1,53	< 0,0001

CPB CABG = cardiopulmonary bypass coronary artery bypass surgery
OP CABG = off pump coronary artery bypass surgery.

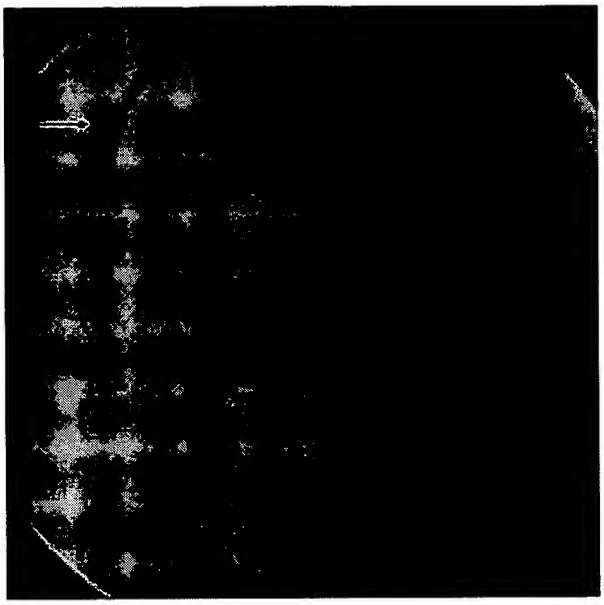

Figure 3. Angiography of a patient post revascularisation: the arrow shows the point of the anastomosis of the radial artery with the proximal part of the right internal thoracic artery.

internal mammary artery stump from a patient's coronary arteriogram in the context of an angiographic study for the evaluation of graft patency on the beating heart, that is in progress in our Laboratory.

Discussion

Off-pump CABG on the beating heart tends to become a routine operation for most cardiosurgical centers[11,14-16]. The development of mechanical stabilizers that stabilize the field to be revascularized, now enables the anastomosis to be performed with excellent precision, avoiding any complications of CPB. However, up to now, one of the main disadvantages of the technique is the difficulty of its application in bypassing arteries of the inferior and posterior wall of the left ventricle.

In this study, we have included patients that were operated on following the new technique without excluding patients with right and circumflex coronary artery disease. We have shown in the past that the revascularization of these areas is possible with excellent immediate results[13]. The quality of the anastomosis using the technique of "verticalization" of the heart, i.e. its displacement towards the midline and upwards, has been evaluated angiographically by Cartier et al[15] on 12 patients and the graft blood flow

was found to be excellent according to standard criteria.[17]

Our results show that the immediate post-operative mortality for the two techniques and the incidence of MI during the first 30 post-operative days did not differ significantly (2% vs 0.4%, and 2.5% vs 1.1%, respectively), although there was a decreasing trend for Group B possibly due to the need for a larger sample in order to demonstrate such differences. These findings are in accordance with other large studies[11,14], although the rates differ, perhaps due to the presence of differences as regards the basic clinical characteristics of the patients studied. It is worthwhile mentioning that in our study we included patients consecutively and excluded only those patients for whom it was impossible to collect and record any post-operative data.

It is important to point out the significant difference of the two techniques regarding the incidence of post-operative stroke. Other studies have demonstrated differences in the incidence of cerebral events, but without reaching any statistically significant differences[11]. Since the appearance of such events is directly related to the presence of extensive atheromatosis of the ascending aorta and the carotids, larger multi-center studies may be needed to demonstrate such differences, although most researchers would agree upon the fact that the ischemic attacks are rather rare for operations on the beating heart.

The differences in the administration of inotropic drugs, intubation time and transfusion requirements were significant. Group B patients clearly needed less inotropic solutions and blood transfusions after the operation, a finding that is consistent with that of other researchers[11].

As regards the biochemical parameters, we observed a significant difference in CK-MB values for patients operated on the beating heart. Although this finding is directly related to the number of perioperative MIs, it seems that the cardioplegia administered to patients on whom CPB is used, greatly affects the post-operative increase of myocardial enzymes. The difference in post-operative creatinine values of the patients of two groups is also significant. There are several causes of the post-operative renal dysfunction, including the use of CPB, the hypoperfusion of the kidneys and the release of substances with a toxic effect on kidneys[18]. The renal function is a parameter that has been recently studied and the data to-date show a clear superiority of off-pump surgery on the beating heart versus CPB surgery with respect to maintenance of normal creatinine clearance values[19].

In conclusion, our study shows that off-pump surgery on the beating heart can be safely performed on the majority of patients. Compared to the use of CPB, patients develop fewer complications and have a better post-operative biochemical profile. In particular, the beating heart is related to a dramatic decrease in the development of post-operative ischemic attacks and the length of stay of the patients in the ICU and in the hospital in total. During the last 2 years, the technique has been applied in our hospital to 94% of our patients and 1250 subjects had been operated on the beating heart by December 2000. What remains to be confirmed is the quality of the anastomoses and the long-term patency of the grafts, i.e. two parameters that are the subject of reserch for many centers, including our own.

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Glossary

Term definitions were acquired from many sources, chiefly, Resources For Optimal Care Of The Injured Patient: 1999 by the Committee on Trauma American College of Surgeons, and Taber's Cyclopedic Medical Dictionary by F. A. Davis Company.

[A] B C DE FG HI J-O P-R S-Z

ATLS
Advanced Trauma Life Support course by the American College of Surgeons.

Aspirate
Refers to accidentally inhaling a substance other than air, such as sucking food, mucous or blood into the airway.

Angiogram
An X-ray of an artery injected with radiopaque dye through a catheter.

Arrhythmia
Any deviation from a normal heart beat.

Aphasia
Loss of the ability to verbally express oneself and/or to understand language.

Anticoagulant
A substance that prevents or delays clotting of the blood.

Anoxia
A lack of oxygen, which can cause damage to the brain.

Anhidrosis
The abnormal absence of sweat.

Angiography
This is a test performed to highlight the outlines of the heart and blood vessels to see if there are any blockages or malformations.

Aneurysm
A balloonlike swelling in the wall of a blood vessel.

Anastomosis
The surgical joining of two ducts or blood vessels to allow flow between them.

Anaphylaxis
An extreme allergic reaction; an acute, generalized, and violent antigen-antibody reaction that can be rapidly fatal.

Amnesia
This is a loss of memory caused by brain damage, or severe emotional trauma.

Air Embolism
When a vein is open, especially if the pressure inside that vein is low, air can enter the blood stream and may reach the heart or the brain. It occurs mostly after a lung injury and can be fatal.

Agonal
A word used to describe a major negative change in a patient's condition, usually preceding immediate death, such as a complete cessation of breathing or a dire change in the patient's EEG or EKG.

ALS
This is a certain level of training. Among other procedures, ALS providers are able to administer certain resuscitation techniques, such as intubation, intravenous access and cardiac monitoring.

AMI
Heart attack; death and subsequent necrosis of the heart muscle caused by inadequate blood supply.

Acute
Sharp, severe, having sudden onset and short course. Sudden, intense flare-up.

ACS
American College of Surgeons; a national organization that evaluates trauma centers.

ACGME
Accreditation Council for Graduate Medical Education.

Acetabulum
The 'cup' that holds the head or 'ball' of the thighbone.

ACEP
American College of Emergency Physicians.

Abrasion
A superficial injury to the skin or other body tissue caused by rubbing or scraping resulting in an area of body surface denuded of skin or mucous membrane. May indicate a site with bone or organ injuries underneath.

ABG
Arterial blood gas reading. A test that analyses arterial blood for oxygen, carbon dioxide and bicarbonate content in addition to blood pH. Used to test the effectiveness of respiration.

Abbreviated Injury Scale (AIS)
An anatomical ranking system for the life-threatening severity of a single injury by body region. An injury is ranked from 1 to 6: 1 - minor, 2 - moderate, 3 - severe non-life-threatening, 4 - severe life-threatening, 5 - critical, and 6 - unsurvivable.

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The Symmetry™ Bypass System Aortic Connector

The Symmetry™ Bypass System Aortic Connector is the first in a line of sutureless anastomoses devices for coronary artery bypass grafting (CABG) developed by St. Jude Medical, Inc. Cardiac Surgery Division - Anastomotic Technology Group (ATG), formerly Vascular Science, Inc. (VSI). St. Jude Medical completed the acquisition of VSI in September of 1999.

In CABG surgery, the anastomosis, or the suturing of the graft to the aorta and the coronary artery, is usually the most difficult, time consuming and critical part of the bypass procedure. The Symmetry™ Bypass System Aortic Connector is a mechanical anastomosis device that allows cardiac surgeons to attach saphaneous vein grafts to the aorta without sutures. The Aortic Connector requires no cross clamping or side biting during deployment.

ATG is developing a complete line of mechanical connectors and delivery systems to address a $1 billion-plus market. This technology may ultimately lead to the elimination of cardiopulmonary bypass and aortic manipulation (cross clamping and/or side biting), facilitating true off-pump procedures.

WINDHOVER INFORMATION INC Health Care Business Intelligence

Lining Up Anastomosis Opportunities

(A#2002900049)

Written By: David Cassak

Issue: *Start-Up: Windhover's Review of Emerging Medical Ventures*, 03/01/2002, page 1

Section: Venture Round (Short Article approx: 524 words)

Article Type: Short Takes

Industry Segment: Supplies, Equipment and Devices/Surgical Equipment & Devices; Supplies, Equipment and Devices/Surgical Equipment & Devices/Minimally Invasive, Least Invasive

Subject/Market Dynamic: Big Vs. Small Company; Device Innovation

Market/ Customer: Hospital Market; Physician Specialty; Physician Specialty/Cardiology

Therapeutic Categories: Cardiovascular

Geography: North America/USA

Companies: Abbott Laboratories Inc.; Abbott Laboratories Inc./Perclose Inc.; Coalescent Surgical Inc.; Johnson & Johnson; Johnson & Johnson/Ethicon Inc.

Summary: As penetration of minimally-invasive cardiac surgery has slowed, anastomosis devices have become a hot technology, since further growth of this promising procedure depends on surgeons' ability to do patent anastomoses on a beating heart. That's why anastomosis companies have been among the hottest properties at the last two Cardiothoracic Techniques & Technologies meetings.

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NCIIA FUNDED ADVANCED E-TEAMS

Advanced E-Team Grant Profile

Simple Anastomosis Device Team

Stanford University, 1999
$20,000.00

The standard method surgeons use to join grafted blood vessels to host vessels in cardiac bypass surgery is called hand suturing. This procedure creates a tight seal but is a lengthy procedure and is subject to a "purse-string effect," a common cause of bypass surgery failure. In most cases, the heart must be arrested during the procedure, leading to poor recovery and multiple complications. The team is funded to develop and prototype a device that joins grafted blood vessels to host vessels in cardiac bypass surgery. The technology that the team is developing joins the vessels without complicated maneuvers that are difficult to perform on a beating heart. The procedure requires only 15 seconds to implant the device and establishes the required "intima to intima contact" (the inside of one vessel to the inside of another vessel) between the anastomosed vessels.

The device is low cost and straightforward to manufacture. Due to its simplicity, surgeons can easily adopt the device and method since it does not require extensive training. The device that the team has designed allows for minimally invasive surgery and would have fewer complications than other options.

The team plans to create a prototype of the device, test its efficiency in vitro, and license the patent rights to a company for further device development and manufacturing. The PI is a cardiac surgeon and the team has an impressive membership including MD/Ph.D. candidates, advisors from industry and the office of technology transfer.

Key Faculty

Bobby Robbins, Principal Investigator, Cardiothoracic Surgery Department, School of Medicine

Mary Palmer, Administrative Contact, Research Management Group

Jessica Smith, Principal Investigator, Office of Technology Licensing

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If you have further comments or want more information, please contact us.

1: J Thorac Cardiovasc Surg. 2004 May;127(5):1421-6.

Early bypass occlusion after deployment of nitinol connector devices.

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BACKGROUND: Reducing the negative side effects associated with extracorporeal circulation is the major advantage of off-pump revascularization. However, side clamping of a calcified aorta for proximal anastomoses can cause emboli, resulting in neurologic damage. This problem has been addressed by introducing a mechanical anastomosis device (Symmetry, St Jude Medical) that allows vein-to-aorta anastomosis without manipulating the aorta. This report describes our experience with this device. METHODS: Between June 2001 and April 2002, 77 connectors (1.3 per patient) were deployed in 61 patients (51 men and 10 women; mean age, 68 +/- 8.6 years) undergoing off-pump coronary artery bypass grafting or beating-heart revascularization. Intraoperative quality assessment included transit-time flow measurement (Medistim) and indocyanine green-based angiography (Spy, Novadaq). RESULTS: The surgeons were meticulously trained in loading of the device. No postoperative neurologic deficits were detected. Fifty-three patients had an uneventful course. However, 8 (13.1%) patients with 12 implanted connectors were symptomatic within 8 months (1 day to 8 months). Angiography revealed significant (95%) stenosis or even occlusion of the proximal vein-to-aorta anastomosis at the level of all connectors. Four patients underwent reoperation (2 dilated-stented and 2 treated with drugs). CONCLUSION: On the basis of these observations, the routine use of the connector was halted at our institution. At the moment, the use of this therapy is reserved for patients with severely calcified aortas with no technical alternative. Further investigations appear necessary to evaluate the clinical patterns of this otherwise promising technology.

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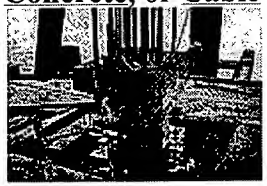
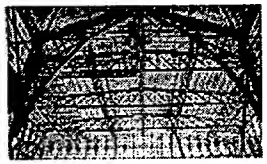
Type of Structures: Steel, Concrete, Arches, & Cables

Types of Structures

The materials used by a Structural Engineer are wide and varied. As a result, there are are many types of structures. However, the main components of most structures are Steel, Concrete, or Cable members. In most structures, the construction is a combination of these elements. A cable bridge, for example, will usually consist of cables (steel), attached to supporting beams (steel), supporting the bridge deck (concrete), sitting on a foundation at either end (concrete). What a beautiful ensemble!!

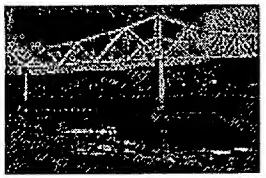


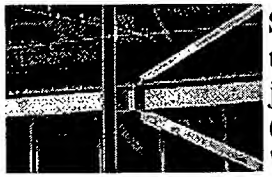
Steel Construction



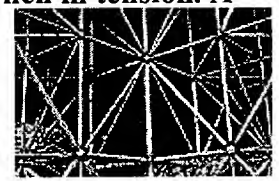
Steel is a wonderful invention. It is very strong for its weight, and relatively inexpensive and available for its strength. Many Structural Engineers dedicate their careers to the design of steel structures. A large steel structure, with beams and trusses and girders of awesome proportions, is truly an inspiring site.

Steel is also the material of choice for commercial or industrial truss construction. A truss is simply a combination of bars linked together to form a series of small triangles. Because of this geometry, trusses can provide very high stability over long distances with relatively little weight.

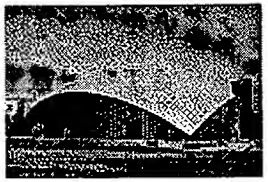




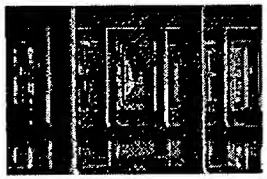
Steel joint construction, whether within a truss or not, utilizes the properties of compression and tension to support a structure. Steel is one of the strongest materials available when in tension. A joint is said to be in 'equilibrium' when the sum of all the forces pushing (compression) and pulling (tension) the joint is equal to zero. This state of 'equilibrium' is what Structural Engineers design for within a structure - to make each and every joint balance to zero. If any of the joints aren't at zero, they will move until they either reach equilibrium or fail.



Concrete Construction

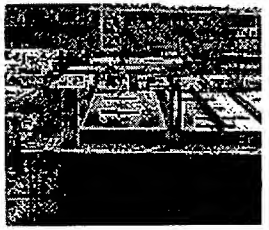


Concrete is an Engineers modeling clay. It can be molded and shaped into beautiful, artistic, and useful structures. It has amazing strength in compression, and since it's basic components are water and sand or gravel, it is extremely inexpensive.



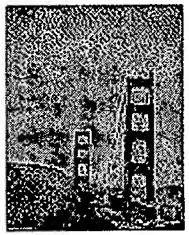
As with steel, whole careers are dedicated to the development of new and improved concrete mixes, utilizing new polymer and fibrous additives, plasticizers, lightweight aggregates, and even recycled materials.

The use of concrete in construction dates back to Roman times, but the modern practice of using 'Reinforced Concrete' in construction is new to this century. Using steel rebar embedded within a concrete beam, column, or slab utilizes the tensile strength of the steel in conjunction with the compressive strength of the concrete to make a stronger, safer structure.

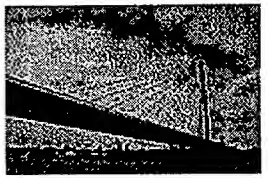


An excellent example of the use of concrete to revolutionize construction is the move towards using more and more reinforced concrete in the construction of long-span bridges. Concrete is so useful, lending itself and its strength to be formed in any shape a mold can be created in, and this ease of construction leads to some extremely attractive, strong, and useful structures. Bridges are now spanning record distances with higher safety factors than ever before, thanks in large part to the use of concrete.

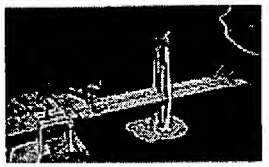
Cable Bridges



Cable structures are some of the most beautiful and recognized structures in engineering. The Golden Gate Bridge, in San Francisco, California, has become a dominant image of



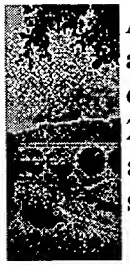
Cables make use of the tensile strength of steel, and can support incredible forces for their size. However, they have no strength at all in compression - pushing on a cable is a little like pushing on a wet noodle -



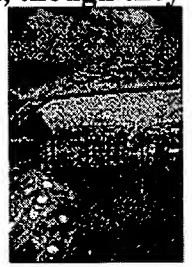
beauty, strength, and engineering; it is also a cable supported (suspension) bridge.

and so are used almost exclusively in suspension structures.

Arch Bridges

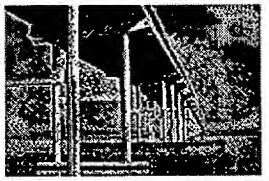


Arches have been, historically and in modern times, an industry standard for stable construction, though they are used as the main support structure most often in bridge spans. One of the enduring images of the great Roman empire in Europe is that of the great aqueduct constructed by the Romans 2000 years ago: it is a series of stone arches supporting a stone and mortar water channel. The aqueduct is still in use in some areas of Europe. Arches can be constructed of many materials - stone, wood, concrete, or steel.



Beam Bridges

Beam supported construction of bridges is the first and foremost style of bridge building; simply laying a straight member between two supports and traveling across the member.



Today's beam structures are somewhat more sophisticated than the traditional 'log across the creek' approach, however. Utilizing pre-stressed members, new materials, and innovative reinforced concrete mixes, spans are becoming steadily longer and at the same time more safe and usable for the public.

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